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Maingot's
ABDOMINAL OPERATIONS
Thirteenth Edition

Editors

Michael J. Zinner, MD, FACS
CEO and Executive Medical Director
Miami Cancer Institute
Miami, Florida
Moseley Professor of Surgery, Emeritus
Harvard Medical School
Boston, Massachusetts

Stanley W. Ashley, MD, FACS
Frank Sawyer Professor of Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

O. Joe Hines, MD, FACS
Professor and Chief
Division of General Surgery
Robert and Kelly Day Chair in General Surgery
Vice Chair for Administration
Department of Surgery
David Geffen School of Medicine
University of California at Los Angeles
Los Angeles, California

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Index
Cameron M. Akbari, MD, MBA, FACS
Senior Attending Physician, Vascular Surgery
Director, Vascular Diagnostic Laboratory
Medstar Washington Hospital Center
Washington, DC

Marco E. Allaix, MD, PhD
Assistant Professor in General Surgery
Department of Surgical Sciences
University of Torino
Torino, Italy

Mohammed Al-Mahroos, MD
Fellow, Minimally Invasive Surgery
McGill University
Montreal, Quebec, Canada

Waddah B. Al-Refaie, MD, FACS
John S. Dillon Professor and Chief of Surgical Oncology
MedStar Georgetown University Hospital
Georgetown Lombardi Comprehensive Cancer Center
Washington, DC

Marshall S. Baker, MD, MBA
Clinical Associate Professor of Surgery
Loyola University Chicago
Stritch School of Medicine
Maywood, Illinois

**Christopher Baron, MD**  
Assistant Professor  
Department of Interventional Radiology  
Vanderbilt University Hospital  
Nashville, Tennessee

**Barbara Lee Bass, MD**  
Bookout Distinguished Presidential Endowed Chair  
Chair, Department of Surgery  
Houston Methodist Hospital  
Professor of Surgery  
Weill Cornell Medical College and Houston Methodist Institute for Academic Medicine  
Full Member  
Houston Methodist Research Institute  
Houston, Texas

**Andrew Bates, MD**  
Department of Surgery  
Stony Brook University Hospital  
Stony Brook, New York

**Kevin E. Behrns, MD**  
Vice President Medical Affairs  
Dean, School of Medicine  
St. Louis University  
St. Louis, Missouri

**Robert D. Bennett, MD**  
Resident in General Surgery  
Department of Surgery  
University of South Florida  
Tampa, Florida
Marc G. H. Besselink, MD, MSc, PhD
Professor of Pancreatic and Hepatobiliary Surgery
Department of Surgery, Cancer Center Amsterdam
Amsterdam UMC, University of Amsterdam
Amsterdam, the Netherlands

Camille Blackledge, MD
Fellow, Division of Gastrointestinal Surgery
Department of Surgery
University of Alabama at Birmingham School of Medicine
Birmingham, Alabama

Jeffrey A. Blatnik, MD
Assistant Professor of Surgery
Department of Surgery, Section of Minimally Invasive Surgery
Washington University School of Medicine
St. Louis, Missouri

Ronald Bleday, MD
Chief
Section of Colon and Rectal Surgery
Associate Chair for Quality and Safety
Department of Surgery
Brigham and Women’s Hospital
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Liliana G. Bordeianou, MD, MPH
Chair, Colorectal Surgery Center
Massachusetts General Hospital
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Stefan A. W. Bouwense, MD, PhD
Fellow, Gastrointestinal Surgery  
Radboud University Medical Center  
Department of Surgery  
Nijmegen, the Netherlands  

Joshua A. Boys, MD  
Cardiothoracic Surgery Fellow  
General Thoracic Surgery Section  
University of Virginia Department of Surgery  
Division of Cardiothoracic and Vascular Surgery  
University of Virginia School of Medicine  
Charlottesville, Virginia  

Elizabeth Breen, MD  
Colon and Rectal Surgeon  
Lahey Hospital and Medical Center  
Program Director  
Colon and Rectal Surgery Residency  
Lahey Hospital and Medical Center  
Burlington, Massachusetts  

L. D. Britt, MD, MPH, DSc (Hon), FACS, FCCM, FRCSEng(Hon),  
FRCSEd(Hon), FWACS(Hon), FRCSI(Hon), FSC(SA)(Hon),  
FRCS(Glasg)(Hon)  
Henry Ford Professor and Edward J. Brickhouse Chairman  
Eastern Virginia Medical School  
Norfolk, Virginia  

David C. Brooks, MD, FACS  
Director of Minimally Invasive Surgery  
Senior Surgeon  
Brigham and Women’s Hospital  
Associate Professor of Surgery Harvard Medical School  
Boston, Massachusetts  

L. Michael Brunt, MD
Section Chief, Minimally Invasive Surgery
Department of Surgery
Washington University School of Medicine
St. Louis, Missouri

**Raphael Bueno, MD**
Fredric G Levin Distinguished Chair in Thoracic Surgery and Lung Cancer Research
Chief, Division of Thoracic Surgery
Co-Director, The Lung Center and the Lung Research Center
Brigham and Women’s Hospital
Professor of Surgery
Harvard Medical School
Boston, Massachusetts

**Jessica Burgess, MD, FACS**
Assistant Professor
Department of Surgery
Eastern Virginia Medical School
Norfolk, Virginia

**Freddy Caldera, DO, MS**
Assistant Professor
Department of Gastroenterology and Hepatology
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

**Michael J. Cavnar, MD**
Assistant Professor
Department of Surgery
Section of Surgical Oncology
University of Kentucky
Lexington, Kentucky

**Nikolaos A. Chatzizacharias, MD, PhD**
Medical College of Wisconsin
Milwaukee, Wisconsin

**Kathleen K. Christians, MD**  
Medical College of Wisconsin  
Milwaukee, Wisconsin

**Thomas E. Clancy, MD**  
Division of Surgical Oncology  
Brigham and Women’s Hospital  
Dana-Farber Cancer Institute  
Assistant Professor of Surgery, Harvard Medical School  
Boston, Massachusetts

**Jordan M. Cloyd, MD**  
Assistant Professor of Surgery  
Division of Surgical Oncology  
The Ohio State University Wexner Medical Center  
Columbus, Ohio

**Dorin Colibaseanu, MD**  
Vice Chair of Education  
Department of Surgery  
Assistant Professor of Surgery  
Mayo Clinic  
Jacksonville, Florida

**Zara Cooper, MD, MSc, FACS**  
Associate Professor  
Department of Surgery  
Associate Chair of Faculty Development  
Department of Trauma Burn and Surgical Critical Care  
Brigham and Women’s Hospital  
Boston, Massachusetts

**Ronald P. DeMatteo, MD, FACS**  
John Rhea Barton Professor and Chair
Department of Surgery
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Tom R. DeMeester, MD
The Jeffrey P. Smith Professor of General and Thoracic Surgery
Chairman
Department of Surgery, Emeritus
Keck School of Medicine
University of Southern California
Los Angeles, California

Daniel T. Dempsey, MD, MBA
Professor of Surgery
Perelman School of Medicine
University of Pennsylvania
Assistant Director of Perioperative Services
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Mary E. Dillhoff, MD, MS
Assistant Professor of Surgery
Department of Surgery
The Ohio State University
Columbus, Ohio

Justin B. Dimick, MD, MPH
George D. Zuidema Professor of Surgery
Chief of the Division of Minimally Invasive Surgery
Director, Center for Healthcare Outcomes and Policy
Associate Chair for Strategy and Finance
Department of Surgery, University of Michigan
Ann Arbor, Michigan

Kristofell R. Dumon, MD, FACS
Associate Professor of Surgery  
Department of Surgery  
Hospital Penn Medicine  
Philadelphia, Pennsylvania

**Brian J. Dunkin, MD, FACS**  
Professor of Surgery  
Weill Cornell Medical College  
John F., Jr. and Carolyn Bookout Chair in Surgical Innovation & Technology  
Medical Director  
Houston Methodist Institute for Technology, Innovation, and Education (MITIE)  
Houston Methodist Hospital  
Houston, Texas

**Barish Edil, MD, FACS**  
Associate Professor of Surgery  
Chief, Section of Surgical Oncology  
University of Colorado at Denver  
Denver, Colorado

**Timothy Eglinton, MBChB, MMedSc, FRACS, FACS, FCSSANZ**  
Associate Professor  
Department of Surgery  
University of Otago  
Christchurch, New Zealand

**Fritz C. Eilber, MD**  
Professor of Surgery  
Professor of Molecular and Medical Pharmacology  
Director UCLA—JCCC Sarcoma Program  
UCLA Division of Surgical Oncology  
Los Angeles, California

**E. Christopher Ellison, MD**  
Academy Professor
Robert M. Zollinger Professor Emeritus
Department of Surgery
The Ohio State University College of Medicine
Columbus, Ohio

**Douglas B. Evans, MD**
Professor and Chair
Department of Surgery
Medical College of Wisconsin
Milwaukee, Wisconsin

**Douglas G. Farmer, MD, FACS**
Professor of Surgery
Surgical Director, Pediatric Liver Transplantation
Surgical Director, Intestinal Transplantation
Division of Liver and Pancreas Transplantation
David Geffen School of Medicine at UCLA
Los Angeles, California

**Liane S. Feldman, MD**
Steinberg-Bernstein Chair of Minimally Invasive Surgery and Innovation
McGill University Health Centre
Director, Division of General Surgery
McGill University
Montreal, Quebec, Canada

**Alessandro Fichera, MD, FACS, FASCRS**
Professor and Division Chief Gastrointestinal Surgery
Department of Surgery
University of North Carolina
Chapel Hill, North Carolina

**Robert J. Fitzgibbons, Jr., MD, FACS**
Harry E. Stuckenhoff Professor and Chairman
Department of Surgery
Creighton University School of Medicine
Co-editor in Chief, *Hernia*
CHI Health Creighton University-Bergan Mercy
Omaha, Nebraska

**James W. Fleshman, Jr., MD**
Sparkman Endowed Chair in Surgery
Chairman, Department of Surgery
Baylor University Medical Center
Professor of Surgery
Texas A&M Health Science Center
Dallas, Texas

**Eugene F. Foley, MD, FACS**
Susan Behren’s MD, Professor and Chair of Surgical Education
Vice Chair for Education
Chief, Division of Colon and Rectal Surgery
Department of Surgery
University of Wisconsin
Madison, Wisconsin

**Yuman Fong, MD, Sc.D. (Hon)**
Chairman
Department of Surgery
City of Hope Medical Center
Duarte, California

**Gerald M. Fried, MD**
Edward W. Archibald Professor and Chair
Department of Surgery
McGill University
Surgeon-in-Chief, McGill University Health Centre
Montreal, Quebec, Canada

**Frank A. Frizelle, MBChB, MMedSci, FRACS, FACS, FASCRS, FRCSI (Hon), FNZMA**
Professor Head of University Department of Surgery
Csaba Gajdos, MD, FACS
Clinical Associate Professor of Surgery
Department of Surgery
Jacobs School of Medicine and Biomedical Science
Buffalo, New York

Sunil K. Geevarghese, MD, MSCI, FACS
Medical Director, Acute Operations and Transplant Perioperative Services
Program Director, Vanderbilt ASTS Transplant and Hepatobiliary Surgery Fellowship
Associate Professor of Surgery, Radiology and Radiological Sciences
Division of Hepatobiliary Surgery and Liver Transplantation
Vanderbilt University Medical Center
Nashville, Tennessee

Kristina L. Go, MD
Chief Resident
University of Florida
Department of Surgery
Gainesville, Florida

Jason S. Gold, MD
Chief of Surgical Oncology, VA Boston Healthcare System
Associate Professor of Surgery
Harvard Medical School
Brigham and Women’s Hospital
West Roxbury, Massachusetts

Joel Goldberg, MD, MPH, FACS
Assistant Professor of Surgery
Harvard Medical School
Colon and Rectal Surgery
Jacob A. Greenberg, MD, EdM
Associate Professor of Surgery
General Surgery Residency Program Director
University of Wisconsin
Department of Surgery
Madison, Wisconsin

Douglas W. Hanto, MD, PhD
Deputy Chief of Surgery
VA St. Louis Health Care System
St. Louis, Missouri
Lewis Thomas Professor of Surgery Emeritus
Harvard Medical School
Boston, Massachusetts

David Harris, MD
Clinical Fellow in Surgery (EXT)
Brigham and Women’s Hospital
Department of Surgery
Boston, Massachusetts

Rian M. Hasson Charles, MD
Assistant Professor of Surgery
Department of Surgery, Section of Thoracic Surgery
Dartmouth-Hitchcock Medical Center
Geisel School of Medicine at Dartmouth
Lebanon, New Hampshire

Alexander T. Hawkins, MD, MPH
Assistant Professor of Surgery
Vanderbilt University Medical Center
Nashville, Tennessee
Mary T. Hawn, MD, MPH  
Professor, Chief of Gastrointestinal Surgery  
Department of Surgery  
University of Alabama at Birmingham School of Medicine  
Birmingham, Alabama

O. Joe Hines, MD, FACS  
Professor and Chief  
Division of General Surgery  
Robert and Kelly Day Chair in General Surgery  
Vice Chair for Administration  
Department of Surgery  
David Geffen School of Medicine  
University of California at Los Angeles  
Los Angeles, California

Ronald B. Hirschl, MD, MS  
Professor of Pediatric Surgery  
Department of Surgery  
Mott Children’s Hospital  
University of Michigan  
Ann Arbor, Michigan

Richard A. Hodin, MD  
Chief of Academic Affairs  
Department of Surgery  
Massachusetts General Hospital  
Professor of Surgery, Harvard Medical School  
Boston, Massachusetts

Nicole J. Look Hong, MD, MSc, FRCSC  
Division of Surgical Oncology  
Sunnybrook Health Sciences Centre  
Assistant Professor of Surgery  
University of Toronto
Toronto, Canada

**Young K. Hong, MD**
Surgical Oncology Fellow
Division of Surgical Oncology
University of Louisville
Louisville, Kentucky

**John G. Hunter, MD, FACS**
Executive Vice President and Chief Executive Officer, OHSU Health System
Mackenzie Professor, OHSU School of Medicine
Oregon Health & Science University
Portland, Oregon

**Roger D. Hurst, MD**
Professor of Surgery
University of Chicago
Pritzker School of Medicine
Chicago, Illinois

**Andrew M. Ibrahim, MD, MSc**
Robert Wood Johnson Clinical Scholar
Institute for Healthcare Policy & Innovation, University of Michigan House Staff, General Surgery University Hospitals Case Medical Center
Ann Arbor, Michigan

**Jennifer L. Irani, MD**
Assistant Professor of Surgery
Harvard Medical School
Associate Surgeon, General and Gastrointestinal Surgery
Brigham and Women’s Hospital and Dana-Farber Cancer Institute
Boston, Massachusetts

**Janeen R. Jordan, MD**
Critical Care (Intensivist)
General Surgery
Orange Park Surgical Associates
Orange Park, Florida

Edward Kelly, MD, FACS
Assistant Professor of Surgery
Department of Trauma Burn and Surgical Critical Care
Brigham and Women’s Hospital
Boston, Massachusetts

Gregory D. Kennedy, MD, PhD
John H. Blue Chair in General Surgery and Professor of Surgery
Director, Division of Gastrointestinal Surgery
University of Alabama at Birmingham School of Medicine
Birmingham, Alabama

Teresa S. Kim, MD
Assistant Professor
Surgical Oncology, Department of Surgery
University of Washington
Seattle, Washington

Cindy Kin, MD, MS, FACS, FASCRS
Assistant Professor of Surgery
Stanford University Department of Surgery
Stanford, California

Jonathan C. King, MD
David Geffen School of Medicine at UCLA
Department of Surgery
Los Angeles, California
Santa Monica General Surgery
Santa Monica, California

Simon Law, MBBChir (Cantab), MA, MS (HK), PhD (HK), FRCSEd, FCSHK, FHKAM, FACS
Cheung Kung-Hai Endowed Chair
Chair Professor in Esophageal and Upper Gastrointestinal Surgery
Department of Surgery
The University of Hong Kong
Hong Kong, the People’s Republic of China

**Christina W. Lee, MD**
Resident Physician
University of Wisconsin School of Medicine and Public Health
Department of Surgery
Madison, Wisconsin

**Yu Liang, MD**
Assistant Professor
Department of General Surgery
UConn Health
Farmington, Connecticut

**Keith D. Lillemoe, MD**
Surgeon-in-Chief
Chief, Department of Surgery
Massachusetts General Hospital
W. Gerald Austen Professor of Surgery
Harvard Medical School
Boston, Massachusetts

**Anne Y. Lin, MD, MSHS**
Assistant Professor of Surgery
Department of Surgery
Section of Colon and Rectal Surgery
University of California Los Angeles
Los Angeles, California

**Natalie Liu, MD**
General Surgery Resident
University of Wisconsin
Department of Surgery
Madison, Wisconsin

**Benjamin P.T. Loveday, MBChB, PhD, FRACS**
Senior Lecturer in Surgery
University of Auckland
Consultant HBP Surgeon
Auckland City Hospital
Auckland, New Zealand

**Arin L. Madenci, MD, MPH**
Resident, General Surgery
Brigham and Women’s Hospital
Harvard Medical School
Boston, Massachusetts

**Najjia N. Mahmoud, MD**
Emilie and Roland T. DeHellebranth Professor of Surgery
Chief, Division of Colon and Rectal Surgery
University of Pennsylvania Health System
Philadelphia, Pennsylvania

**Jeffrey B. Matthews, MD, FACS**
Dallas B. Phemister Professor of Surgery and Chairman
Department of Surgery
The University of Chicago
Chicago, Illinois

**Martin McCarter, MD, FACS**
Professor of Surgery, Section of Surgical Oncology
University of Colorado at Denver
Denver, Colorado

**David W. McFadden, MD, MBA**
Murray-Heilig Professor and Chairman
Department of Surgery
The University of Connecticut
Farmington, Connecticut

**Fabrizio Michelassi, MD**
Lewis Atterbury Stimson Professor  
Chairman, Department of Surgery  
Weill Cornell Medicine  
Surgeon-in-Chief  
New York-Presbyterian Weill Cornell Medical Center  
New York, New York

**Fernando Mier, MD**
Division of General and Gastrointestinal Surgery  
Department of Surgery and the Digestive Health Center  
Oregon Health and Science University  
Portland, Oregon

**Jon B. Morris, MD**
The Ernest F. Rosato—William Maul Measey Professor in Surgical Education  
Vice Chair for Education, Department of Surgery Hospital  
University of Pennsylvania  
Philadelphia, Pennsylvania

**Neil J. Mortensen, MA, MBChB, MD, FRCS Eng, Hon FRCPS Glas, Hon FRCS Edin, Hon FRCSI**
Professor of Colorectal Surgery  
Nuffield Department of Surgery  
University of Oxford  
Hon Consultant Surgeon  
Department of Colorectal Surgery, Churchill Hospital  
Oxford University Hospitals, Oxford  
England, United Kingdom

**Amani Munshi, MD, FRCSC, FACS**
Clinical Assistant Professor  
Department of Surgery
University Hospitals, St. John Medical Center
Westlake, Ohio

David L. Nahrwold, MD
Emeritus Professor of Surgery
Department of Surgery
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Heidi Nelson, MD
Fred C. Andersen Professor of Surgery
Chair, Department of Surgery
Mayo Clinic
Rochester, Minnesota

Sanjay Pandanaboyana, MBBS, MPhil, FRCS
Consultant HBP Surgeon
Auckland City Hospital
Auckland, New Zealand

Alessandro Paniccia, MD
Chief Resident in General Surgery
Department of Surgery
University of Colorado Anschutz Medical Campus
Denver, Colorado

Christina M. Papageorge, MD, MS
General Surgery Resident
University of Wisconsin Hospital and Clinics
Department of Surgery
Madison, Wisconsin

Theodore N. Pappas, MD, FACS
Distinguished Professor of Surgical Innovation
Chief of Advanced Oncologic and Gastrointestinal Surgery
Duke University School of Medicine  
Durham, North Carolina  

**Purvi Y. Parikh, MD, FACS**  
Hepato-Pancreato-Biliary Surgeon  
Director, Center of Excellence for HPB Care  
The Permanente Medical Group, Inc.  
Kaiser–Sacramento Medical Center  
Department of Surgery  
Sacramento, California

**Guillaume Passot, MD, PhD**  
Department of Surgical Oncology  
CHU Lyon Sud, Pierre Bénite, France  
Professor of Surgery  
Lyon 1 University  
Lyon, France

**Sameer H. Patel, MD, FACS**  
Department of Surgical Oncology  
The University of Texas MD Anderson Cancer Center  
Houston, Texas

**Marco G. Patti, MD, FACS**  
Professor of Medicine and Surgery  
Co-Director, Center for Esophageal Diseases and Swallowing  
University of North Carolina School of Medicine  
Chapel Hill, North Carolina

**Timothy M. Pawlik, MD, MPH, MTS, PhD, FACS, FRACS (Hon)**  
Professor and Chair, Department of Surgery  
The Urban Meyer III and Shelley Meyer Chair for Cancer Research  
Professor of Surgery, Oncology, and Health Services Management and Policy  
Surgeon in Chief  
The Ohio State University Wexner Medical Center  
Columbus, Ohio
William H. Peranteau, MD
Assistant Professor of Surgery
The Division of Pediatric General, Thoracic, and Fetal Surgery
The Children’s Hospital of Philadelphia
Philadelphia, Pennsylvania

Alexander Perez, MD, FACS
Assistant Professor of Surgery
Chief of Pancreatic Surgery
Duke University School of Medicine
Durham, North Carolina

Silvana Perretta, MD
Professor of Surgery
Department of Digestive and Endocrine Surgery
NHC University Hospital
Director of Education IRCAD-IHU
Strasbourg, France

Henry A. Pitt, MD
Temple University
Philadelphia, Pennsylvania

Jeffrey L. Ponsky, MD, MBA, FACS
Lynda and Marlin Younker Chair in Developmental Endoscopy
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio

Michael J. Pucci, MD, FACS
Associate Professor of Surgery
Sidney Kimmel Medical College of Thomas Jefferson University
Co-Director, Advanced Gastrointestinal Surgery Fellowship
Associate Director, Undergraduate Education
Division of General Surgery, Department of Surgery
Philadelphia, Pennsylvania

Chandrajit P. Raut, MD, MSc, FACS
Associate Surgeon
Division of Surgical Oncology, Brigham and Women’s Hospital
Surgery Director, Center for Sarcoma and Bone Oncology
Dana-Farber Cancer Institute
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Michael M. Reader, MD, FACS
General Surgery
Houston Methodist Surgical Associates
Assistant Professor of Clinical Surgery
Weill Cornell Medical College
Houston, Texas

Diego C. Reino, MD
Cleveland Clinic Florida
Transplant and Hepatobiliary Surgery
Department of Solid Organ Transplantation
Weston, Florida

Joao B. Rezende Neto, MD, PhD, FRCSC, FACS
Associate Professor
Department of Surgery
University of Toronto
Trauma and Acute Care Surgery
Division of General Surgery
St. Michael’s Hospital
Surgeon Investigator—Keenan Research Center for Biomedical Sciences
Toronto, Ontario
Canada

John J. Ricotta, MD, FACS
Clinical Professor of Surgery
George Washington University
Washington, DC

**Patricia L. Roberts, MD**
Chair, Division of Surgery
Senior Staff Surgeon, Department of Colon and Rectal Surgery
Lahey Hospital and Medical Center
Burlington, Massachusetts
Professor of Surgery
Tufts University School of Medicine
Boston, Massachusetts

**Sean M. Ronnekleiv-Kelly**
University of Wisconsin Hospital and Clinics
Department of Surgery
Clinical Science Center
Madison, Wisconsin

**Robert E. Roses, MD**
Assistant Professor
Department of Surgery
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

**Ori D. Rotstein, MD**
Professor and Associate Chair of Surgery
University of Toronto
Surgeon-in-Chief, St. Michael’s Hospital
Toronto, Ontario
Canada

**Daniel Ruan, MD**
General Surgeon
Department of Surgery
Tampa General Hospital
Tampa, Florida

Tara A. Russell, MD, MPH, PhD
Resident Physician
UCLA Department of General Surgery
Los Angeles, California

George A. Sarosi, Jr., MD
Professor and Program Director
Vice Chair of Education
Department of Surgery
University of Florida
Gainesville, Florida

Mitsuru Sasako, MD, PhD
Special Consultant Surgeon
Department of Surgery
Yodogawa Christian Hospital
Osaka
Professor Emeritus
Hyogo College of Medicine
Nishinomiya, Japan

Bruce D. Schirmer, MD
Stephen H. Watts Professor of Surgery
University of Virginia Health System
Department of Surgery
Charlottesville, Virginia

Richard D. Schulick, MD, MBA, FACS
Aragón/Gonzalez-Giustí Endowed Chair
Chair, Department of Surgery
Director, Cancer Center
Professor of Surgery
University of Colorado School of Medicine
Aurora, Colorado
Anthony J. Senagore, MD, MS, MBA
Professor, Vice Chair for Research
Department of Surgery
Western Michigan University - Homer Stryker MD School of Medicine
Kalamazoo, Michigan

Parth K. Shah, MBBS
Fellow in Complex General Surgical Oncology
H. Lee Moffitt Cancer Center
University of South Florida
Tampa, Florida

Brian D. Shames, MD
Associate Professor of Surgery
Division Chief General Surgery
Program Director General Surgery Residency
University of Connecticut School of Medicine
Farmington, Connecticut

Eric G. Sheu, MD, D.Phil
Associate Surgeon
Brigham and Women’s Hospital
Assistant Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Scott A. Shikora, MD, FACS
Professor of Surgery
Harvard Medical School
Director, Center for Metabolic and Bariatric Surgery
Department of Surgery
Brigham and Women’s Hospital
Boston, Massachusetts

Hisashi Shinohara, MD, PhD
Chairman, Upper GI Division
Department of Surgery
Hyogo College of Medicine
Nishinomiya, Japan

Jory S. Simpson, MD, MEd, FRCSC
Assistant Professor
Department of Surgery
University of Toronto
Division of General Surgery
St. Michael’s Hospital
Toronto, Canada

Douglas S. Smink, MD, MPH
Program Director
General Surgery Residency
Associate Chair of Surgery
Department of Surgery
Brigham and Women’s Hospital
Associate Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Kevin C. Soares, MD
Resident in General Surgery
Department of Surgery
The Johns Hopkins School of Medicine
Baltimore, Maryland

Nathaniel J. Soper, MD, FACS
Loyal and Edith Professor and Chairman of Surgery
Surgeon-in-Chief, Northwestern Memorial Hospital
Northwestern Medicine
Chicago, Illinois

Ian S. Soriano, MD, FACS, FASMBS, FPALES
Clinical Assistant Professor of Surgery
Perelman School of Medicine
University of Pennsylvania
Pennsylvania Hospital
Philadelphia, Pennsylvania
Visiting Assistant Professor of Surgery
University of the Philippines College of Medicine
Philippine General Hospital
Manila, Philippines

**David I. Soybel MD, FACS**
David L. Nahrwold Professor of Surgery
Division Chief, General Surgery Specialties & Surgical Oncology
Vice-Chairman (Research)
Department of Surgery
Penn State Hershey Medical Center
Hershey, Pennsylvania

**Shelby J. Stewart, MD**
Assistant Professor
Department of Thoracic surgery
University of Maryland
Baltimore, Maryland

**Steven M. Strasberg, MD**
Prueitt Professor of Surgery
Section of HPB Surgery
Washington University in Saint Louis
Siteman Cancer Center and Barnes-Jewish Hospital
Saint Louis, Missouri

**David M. Straughan, MD**
 Resident in General Surgery
Department of Surgery
University of South Florida
Morsani College of Medicine
Tampa, Florida

Cabrini L. Sutherland, MD, MPH
Acute Care Surgery Service
Trauma Trust
Tacoma, Washington

Lee L. Swanström, MD
Professor of Surgery
The Oregon Clinic
Portland, Oregon

Mark A. Talamini, MD, MBA
Professor and Chair
Department of Surgery
School of Medicine, SUNY Stony Brook
Chief of Surgical Services
Stony Brook Medicine
Stony Brook, New York

Nabil Tariq, MD, FACS
Assistant Professor of Surgery
Department of Surgery
Houston Methodist Hospital
Houston, Texas

Ali Tavakkoli, MD
Interim Chief, Division of General and GI Surgery
Brigham and Women’s Hospital
Co-Director, Center for Weight Management and Metabolic Surgery
Associate Professor of Surgery, Harvard Medical School
Boston, Massachusetts

Ezra N. Teitelbaum, MD, MEd
Assistant Professor of Surgery and Medical Education
Northwestern University
Feinberg School of Medicine
Chicago, Illinois

**Tina Thomas, MD**
Clinical Lecturer, Pediatric Surgery
Research Fellow, Newman Lab
Department of Pediatric Surgery
C. S. Mott Children’s Hospital
University of Michigan
Ann Arbor, Michigan

**Daniel King Hung TONG, MBBS, MS, PhD, FRACS, FACS, FCSHK, FHKAM**
Honorary Clinical Associate Professor
The University of Hong Kong
Hong Kong

**Jennifer F. Tseng, MD, MPH**
Utley Professor and Chair, Department of Surgery
Boston University
Surgeon-in-Chief, Boston Medical Center
Boston, Massachusetts

**Jeff Van Epps, MD**
Fellow
Colon and Rectal Surgery
University of Minnesota
Minneapolis, Minnesota

**Hjalmar C. van Santvoort, MD, PhD**
Hepato-Pancreato-Biliary Surgeon
Associate professor
Regional Academic Cancer Center Utrecht
St. Antonius Hospital Nieuwegein and University Medical Center
Utrecht, the Netherlands
Jean-Nicolas Vauthey, MD, FACS
Professor of Surgery
Chief, Hepato-Pancreato-Biliary Section
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Vic Velanovich, MD
Professor of Surgery
Department of Surgery
University of South Florida
Tampa, Florida

Sharon M. Weber, MD, FACS
Tim and MaryAnn McKenzie Chair of Surgical Oncology
Director for Surgical Oncology
UW Carbone Cancer Center
Professor of Surgery
Department of Surgery
University of Wisconsin
Madison, Wisconsin

Jon O. Wee, MD
Section Chief, Esophageal Surgery
Director of Robotics in Thoracic Surgery
Co-Director of Minimally Invasive Thoracic Surgery
Associate Program Director
Division of Thoracic Surgery
Brigham and Women’s Hospital
Assistant Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Martin R. Weiser, MD
Stuart H. Quan Chair in Colorectal Surgery
Vice Chair, Faculty Affairs
Department of Surgery
Memorial Sloan Kettering Cancer Center
Professor of Surgery
Weill Cornell Medical College
New York, New York

Mark Lane Welton, MD, MHCM
Chief Medical Officer
Fairview Health Services
Professor of Surgery
Section of Colon and Rectal Surgery
University of Minnesota
Minneapolis, Minnesota

Edward E. Whang, MD
Associate Professor of Surgery
Department of Surgery
Brigham and Women’s Hospital
Harvard Medical School
Boston, Massachusetts

John A. Windsor, MD, MBChB, FRACS, FACS, FRSNZ
Professor of Surgery
University of Auckland
Consultant HBP/Upper GI Surgeon
Auckland City Hospital
Auckland, New Zealand

Joyce Wong, MD
Assistant Professor of Surgery
Zucker School of Medicine at Hofstra/Northwell
Lenox Hill Hospital
New York, New York
Yanghee Woo, MD, FACS
Associate Clinical Professor
Vice Chair, International Surgery
Director, GI Minimally Invasive Therapies
Division of Surgical Oncology
Department of Surgery
City of Hope National Medical Center
Duarte, California

Mu Xu, MD, PhD
Resident in Surgery
David Geffen School of Medicine at UCLA
Los Angeles, California

Charles J. Yeo, MD, FACS
Samuel D. Gross Professor and Chairman
Department of Surgery
Jefferson Pancreas, Biliary and Related Cancer Center
Department of Surgery
Sidney Kimmel Medical College
Thomas Jefferson University
Senior Vice President and Enterprise Chair, Surgery
Jefferson Health
Co-Director
Jefferson Pancreas, Biliary, and Related Cancer Center
Co-Editor in Chief, Emeritus
Journal of Gastrointestinal Surgery
Official Publication of the SSAT
Editor in Chief, Journal of Pancreatic Cancer
Philadelphia, Pennsylvania

Heather Yeo, MD, MHS
Assistant Professor of Surgery
Weill Cornell Medical College
Assistant Professor of Public Health
Weill Cornell Medical College
New York, New York

Trevor M. Yeung, MA, MBBChir, D.Phil, FRCS
Specialty Registrar
Department of Colorectal Surgery
Oxford University Hospitals
Oxford, United Kingdom

Herbert J. Zeh, III, MD
University of Pittsburgh Medical Center
Department of Surgery
Pittsburgh, Pennsylvania

Tiffany Zens, MD
University of Wisconsin School of Medicine and Public Health
Department of Surgery
Madison, Wisconsin

Michael J. Zinner, MD, FACS
CEO and Executive Medical Director
Miami Cancer Institute
Miami, Florida
Moseley Professor of Surgery, Emeritus
Harvard Medical School
Boston, Massachusetts
For the editors, the production of the newest edition of *Maingot’s Abdominal Operations* represents a labor of love. *Maingot’s* has always filled a unique niche. This text has consistently offered a comprehensive discussion of surgical diseases of the abdomen with a focus on operative strategy and technique. The book has served as a needed reference to refresh our knowledge before a common operation or in preparation for a novel one. Our intended audience for this edition is the same as for the original publication; the book is meant for the surgical trainee as well as the practicing surgeon, and for the American surgeon as well as for our international colleagues. We continue to have a significant international audience and have made every effort to develop a product that is equally valuable to readers in India as well as Indiana. This is the fifth effort together for the senior editors, joined this time by a new editor (O.J.H.) with a fresh vision; it continues to be not only a pleasure but an honor and a privilege to have the opportunity to co-edit the 13th edition of this classic textbook.

Abdominal surgery has clearly evolved since Rodney Maingot’s first edition of this text in 1940. Not only has our knowledge base increased substantially, but the procedures themselves have become both more complex and less invasive. The current subspecialization in abdominal surgery, a consequence of these changes, continues to challenge the need for a comprehensive text. Abdominal disease has been increasingly parcelled between foregut, hepatobiliary, pancreatic, colorectal, endocrine, acute care, and vascular specialists. The editors continue to believe, however, that the basic principles of surgical care in each of the anatomic regions have more similarities than differences. Experience in any one of these organs can inform and strengthen the approach to each of the others. In fact, in community hospitals and rural settings both nationally and internationally, practices spanning multiple subspecialties remain the norm. Few would
question the need for the abdominal surgeon to be well versed in dealing with any unexpected disease that is encountered in the course of a planned procedure. For many of us, *Maingot’s Abdominal Operations* has consistently helped to fill that need.

This textbook remains primarily disease focused, in addition to maintaining its organ/procedure format. The new edition of this textbook is a significant revision and, in many areas, a completely new book. We have continued to focus some chapters on technical operative procedures, whereas others elucidate new and continuing concepts in diagnosis and management of abdominal disease. The new edition is expanded compared with previous versions, and we have continued to present the opinions and knowledge of more than one expert. In areas where opinions and approaches differ, we have added even more “Perspective” commentaries by experts in the field who we expected might have distinct opinions about approaches and/or operative techniques. In response to recent developments, we have added chapters on quality metrics, enhanced recovery after surgery, and robotic surgery. We have attempted to maintain an international flavor and have included a cross-section of both seasoned senior contributors and new leaders in gastrointestinal surgery. We continue to provide a contemporary textbook on current diagnostic procedures and surgical techniques related to the management and care of patients with all types of surgical digestive disease.

An extensive artwork program was undertaken for this edition. Many line drawings have been recreated to reflect the contributors’ preferred method for performing certain surgical procedures. Some of these drawings are new and give the book a more consistent look. In addition, this edition continues full-color text and color line art.

In the preface to the sixth edition, Rodney Maingot noted, “As all literature is personal, the contributors have been given a free hand with their individual sections. Certain latitude in style and expression is stimulating to the thoughtful reader.” Similarly, we have tried to maintain consistency for the reader, but the authors have also been given a free hand in their chapter submissions.

We would like to thank the publisher, McGraw-Hill, and in particular Christie Naglieri and Andrew Moyer, for their unwavering support during the lengthy time of development of this project. Their guidance was invaluable to completing this project in a single comprehensive volume. Their suggestions and attention to detail made it possible to overcome the innumerable
problems that occur in publishing such a large textbook.

Finally, we want to acknowledge the expertise of each chapter and perspective contributor. Without their effort, this book would not have been possible. We acknowledge our editorial assistant, Linda Smith, who has survived the trials of this book; she has been invaluable, and we never would have been able to do it without her. Patrina Tucker and Heather Couture have also stepped up and made this project possible. We owe them a great debt of gratitude for helping with every step of the work. To all of those who have participated in the creation and publication of this text, we thank you very much.

Michael J. Zinner, MD, FACS
Stanley W. Ashley, MD, FACS
O. Joe Hines, MD, FACS
INTRODUCTION
GASTROINTESTINAL SURGERY: A HISTORICAL PERSPECTIVE

David L. Nahrwold

INTRODUCTION

Surgeons continue to have brilliant ideas and use amazing technology to bring safe and effective surgery to people all over the world, but it was not always so. The evolution of surgery to its present state has taken at least 200 years, and surgery is still evolving. Each of the many abdominal operations surgeons now performed has its own special history, from the idea that spawned it to the present state of its art. Abdominal operations were brought to fruition by innovative surgeons who carefully planned them and had the courage to perform them and the wisdom to modify and improve them.

Although the histories of all abdominal operations are interesting, a broader view of abdominal surgery puts those stories into perspective. The broader view is best obtained by asking: What enabled abdominal surgery to evolve to its present state? What were the barriers to the evolution of abdominal surgery? How were the barriers overcome, and who overcame
them? Although recognizing the individuals who developed and perfected individual operations is important, the perspective of this chapter is on how modern abdominal surgery came about and how it was enabled.

THE EARLY PROBLEMS

Prior to the middle of the 19th century, few operations were done with the expectation that the patient would live and be cured of the disease for which it was performed. The fundamental barrier was the excruciating pain caused by opening the abdomen and manipulating its contents, even when tempered by the administration of alcohol or derivatives of opium such as laudanum and morphine. Patients often died from postoperative bleeding, dehydration, or malnutrition. But it was infection that was the bane of surgeons. Infections followed almost all operations. Wound infection and peritonitis were the killers of patients who had abdominal surgery. Without antibiotics or even standardized methods of dressing infected wounds, the consequences of infection were disastrous. Except in a few isolated instances, physicians knew that surgery was not a realistic therapeutic option until infection, hemorrhage, dehydration, and malnutrition could be alleviated or eliminated. Remarkable progress was made during the second half of the 19th century, enabling surgeons to bring hope to a large number of patients with diseases or conditions that swiftly became amenable to surgery.

ANESTHESIA

The modernization of abdominal surgery was dependent on the patient’s loss of sensation, anesthesia, during the procedure. The development of anesthesia eliminated the cruelty of surgery and enabled surgeons to incise, manipulate, and suture tissue in a disciplined manner without the urgency and disorder that surrounded operations in the conscious patient.

Dr. Crawford Long was the first to use ether for general anesthesia, in 1842, but he did not report it until 1849. Meanwhile, in 1846, the Boston dentist William T.G. Morton demonstrated the use of ether as a general anesthetic in the amphitheater of the Massachusetts General Hospital in a patient with a tumor of the neck, which was removed by Dr. John Collins Warren, former Dean of the Harvard Medical School (1816-1819).
OVERCOMING INFECTION

Louis Pasteur conducted experiments between 1860 and 1864 showing that “pyogenic vibrio” caused puerperal fever and that fermentation of wine and milk did not proceed in the absence of living organisms. Heating milk and wine, now called pasteurization, killed the bacteria, but not the yeast, and made them safe to drink.³

Robert Koch, the German physician and microbiologist who in 1876 identified *Bacillus anthracis* as the cause of anthrax, learned how to grow bacteria on media and, in 1884, isolated *Vibrio cholerae*, the agent that causes cholera. In 1882, Koch identified the slow-growing *Mycobacterium tuberculosis* as the cause of tuberculosis. Between 1879 and 1889, he also isolated the organisms that caused typhoid fever, diphtheria, pneumonia, tetanus, meningitis, and gonorrhea. He found organisms in wound infections. Koch proved that the germs in the germ theory of disease were organisms that could be isolated and identified.⁴

The English physician Joseph Lister, professor of surgery at the University of Glasgow, soaked surgical dressings in carbolic acid (phenol) and applied them to the open leg wound of a boy who had suffered a compound fracture (Fig. 1-1). No infection ensued, and to his surprise, the bones healed solidly together. He published the results in a series of articles in *The Lancet* in 1867. He returned to the University of Edinburgh in 1869 and continued to develop methods of asepsis and antisepsis. Soon, surgeons performed operations under a mist of dilute carbolic acid that was sprayed in the operating room, instruments were dipped in carbolic acid before use, and the surgical wound was covered in dressings saturated with it.⁵ This routine, with variations, became known as listerism, which Joseph Lister introduced to the United States during a visit in 1876.
Surgeons learned from listerism of the need to maintain sterile conditions at the operating table. Although the steam autoclave was invented in 1879, it was not used routinely for sterilization of instruments and supplies until early in the 20th century. Dr. William Halsted, who embraced listerism, introduced the use of surgical gloves at Johns Hopkins Hospital. However, the original use of the gloves made by the Goodyear Company was to protect the hands of the surgical team from the carbolic acid.6

Measures to control infection have been used routinely since the first half of the 20th century and affect hospital construction, all invasive procedures, interactions with patients, and behaviors in hospitals and other medical
facilities.

The medicinal use of sulfa drugs in the late 1930s, the discovery of penicillin in 1928 by Fleming, and its clinical use by Florey and his colleagues in the early 1940s began the successful search for many other antibiotics to combat infections by almost all known bacteria. During the second half of the 20th century and beyond, surgical infections have been ameliorated or cured by the large array of antibiotics that became available, although antibiotic-resistant bacteria from antibiotic overuse have recently become a problem. In recent decades, the evidence-based prophylactic use of antibiotics in abdominal surgery has almost eliminated surgical site infections.

THE SURGEON’S WORKPLACE

Hospitals were built to provide clinical material for the faculties and students of the country’s original medical schools. They included the Pennsylvania Hospital (1752), the New York Hospital (1771), and the Massachusetts General Hospital (1811), all of which became the workplaces of innovative physicians and surgeons who taught and conducted research (Fig. 1-2). However, most cities had no hospitals; instead, almshouses, poorhouses, and poor farms, living facilities for indigent people in the community were established by charitable organizations and wealthy individuals. Over time, many of them became hospitals for the sick and poor. Some physicians also established hospitals, often by converting a large home into a place for their sick patients. Many hospitals were dirty and poorly kept, and because some of the occupants had infectious diseases for which there were no cures, the other occupants also became infected and often died.
Because hospitals were known as dangerous places, middle- and upper-class families kept sick relatives at home. The typical horse-and-buggy doctor made rounds to the homes of his patients, and minor procedures, such as drainage of a carbuncle or suture of a wound, were performed in the home. Occasionally, a physician whose patient was in desperate straits would attempt an abdominal operation on the kitchen table, usually with disastrous results.

As medical diagnosis and treatment advanced, medical care in the home was no longer practical. Beginning in the latter half of the 19th century, religious organizations, civic groups, and municipalities began aggressive programs to build hospitals modeled after those in Europe, and by 1900, there were more than 4000 hospitals in the United States. However, the management, medical staffs, nursing, and other services of these hospitals varied from excellent to poor.

**THE HOSPITAL STANDARDIZATION PROGRAM IMPROVES HOSPITALS**
Dr. Franklin H. Martin, a Chicago gynecologist, led the founding of the American College of Surgeons (ACS) in 1912 (Fig. 1-3). He and other leaders of the ACS were concerned about the marked variation in the quality of hospitals throughout the country and began a program to standardize hospitals in 1916 by establishing standards that hospitals were required to meet. Surveyors visited the hospitals to determine their compliance and to offer help in meeting the standards. The ACS also held annual hospital standardization conferences to educate hospital personnel. The American Hospital Association, which initiated institutional memberships in 1918, also contributed to the modernization of hospital management.

**FIGURE 1-3** Dr. Franklin H. Martin, Founder of the American College of Surgeons. (Image courtesy of the Archives of the American College of Surgeons.)
Only 13% of the 692 hospitals surveyed in 1918 were approved by the ACS, but by 1939, 76% of the 3564 hospitals surveyed were approved. Over the years, the standards proliferated, and in 1951, the ACS transferred the program to what is now The Joint Commission.

The Hospital Standardization Program and The Joint Commission were largely responsible for the current organization and functions of the modern hospital. The standards they set have saved many lives and made surgery safe.

**NURSING AND HOSPITAL ADMINISTRATION**

Although hospitals proliferated early in the 20th century, few of them hired nurses to care for patients. Graduate nurses were hired by middle- and upper-class patients as “special nurses” to care for them in their homes or in the hospital during illnesses. To serve patients who could not afford special nurses, hospitals established schools of nursing in which the students were taught by a faculty of 1 or 2 graduate nurses and the medical staff of the hospital. Student nurses were assigned to wards to care for patients, often with very little supervision. Many of these schools closed during the Great Depression, and later, colleges and universities established degree programs, which now educate most of the country’s nurses. Prior to World War II, the supply of graduate nurses became sufficient for hospitals to hire nursing staffs to care for their patients. As the complexity of medical care escalated, nurses assumed many roles other than hospital care, and they continue to be indispensable to the healthcare system.

During the first half of the 20th century, when hospitals were simple organizations, hospital administrators learned from a mentor or on the job. By the middle of the century, hospitals had become departmentalized and complex, requiring expertise in finance, personnel management, construction, and many other fields of management. This led to the development of advanced degree programs in hospital administration, the first of which was established at the University of Chicago in 1934. Within a few decades, many universities had established such programs.

**APPLYING THE BASIC SCIENCES**
Although the gross structure of the human body and its organs had been delineated by the middle of the 19th century, the functions of organs remained mysterious. Concurrent development of the basic sciences of pathology, microbiology, physiology, and chemistry during the second half of the 19th century led to an understanding of organ function and disease. During this period, Rudolph Virchow, using the ever-improving optics of the microscope, introduced histopathology to the medical sciences, and Friedrich von Recklinghausen described embolism, infarction, tissue degeneration, and many diseases and conditions such as uterine adenomyomata. Improved techniques for fixing, embedding, and staining tissue facilitated more accurate diagnoses in the early 20th century, and the process of preparing frozen sections of tissues, reported by Dr. Louis Wilson of the Mayo Clinic in 1905, enabled pathologists to accurately diagnose diseases during operations.9

New techniques enabled investigators to understand normal and abnormal gastrointestinal physiology. Between the 1890s and his death in 1936, the Russian physiologist Ivan Pavlov used Heidenhain pouches and gastric and esophageal fistulas in dogs to study salivary and gastric secretions as well as conditioned reflexes, work for which he received the Nobel Prize.10 His experiments inspired many surgical investigators to use similar methods to study gastrointestinal hormonal physiology and motility during the 20th century. Their work, and the work of others, resulted in a comprehensive understanding of the biochemistry, physiology, and pharmacology of the hepatobiliary and digestive systems in health and disease.

Army surgeon Dr. William Beaumont performed the first human experiments in gastric physiology during the first half of the 19th century,11 but it was not until Dr. Lester Dragstedt studied gastric secretion in ulcer patients that gastrointestinal physiology was applied to the development of surgical procedures to combat excessive acid secretion. He introduced vagotomy to reduce gastric acid secretion.12 Upon finding that vagotomy inhibited gastric emptying, he and others added pyloroplasty or antrectomy.

Beginning with the administration of intravenous fluids to surgical patients by Dr. Rudolph Matas in 1924, many advances in biochemistry and physiology led to a greater understanding of body composition, nutrition, and fluid, electrolyte, and acid-base balance. The studies of Dr. Francis Moore and others culminated in his magisterial text, *Metabolic Care of the Surgical*
Patient, which taught surgeons how to deliver the highest level of pre- and postoperative care.\textsuperscript{13} Drs. Jonathan Rhoads and Stanley Dudrick emphasized the importance of nutrition in surgical patients and demonstrated that intravenous alimentation could support normal growth and development of puppies and babies.\textsuperscript{14}

The basic science of immunology matured during the 20th century, enabling the first kidney transplantation by Dr. Joseph Murray and his associates in 1954 and the first liver transplantation by Dr. Thomas Starzl in 1963.

**BLOOD, TRAUMA, AND SHOCK**

After Karl Landsteiner identified the major blood groups A, B, and O in 1901, transfusion of blood and blood products became safer. Dr. George W. Crile, professor of surgery at Case-Western Reserve University, and Dr. William Halsted of The Johns Hopkins Hospital employed blood transfusions during surgical procedures. Reactions to transfusions were frequent until 1940, when the Rh system was discovered and taken into account in matching donor blood to patients. Dr. Bernard Fantus established the first hospital blood bank in the United States at Cook County Hospital in Chicago in 1937.\textsuperscript{15}

Liquid and reconstituted dried plasma was used extensively for resuscitation from wounds during World War II. Lessons learned from the Korean conflict, the Vietnam War, and subsequent conflicts have been applied to the management of civilian trauma and burns, especially the techniques of resuscitation from shock, which were studied extensively by Dr. G Thomas Shires and his colleagues.\textsuperscript{16} The wartime concepts of rapid evacuation for resuscitation and early transport to a major healthcare facility are embodied in the existing trauma system in the United States. The military experience has also informed the management of abdominal gunshot and knife wounds and blunt abdominal injuries in the civilian population.

**THE SURGEON’S TOOLS**

More than 200 years have elapsed since Ephraim McDowell performed the first abdominal operation in the United States to remove a huge ovarian
tumor from a woman in Danville, Kentucky.\textsuperscript{17} Subsequently, and especially during the latter half of the 19th century, operations were developed in Europe and the United States to deal with almost every abdominal disease or condition. The need to design and manufacture surgical instruments spawned an entirely new field, biomedical engineering, which became institutionalized in the late 1960s when universities began degree programs in biomedical engineering. The manufacture of surgical instruments and supplies is now vested in a huge industry that produces products ranging from silk sutures to robots.

Manufacture of most surgical instruments was routine by the beginning of the 20th century, including retractors, hemostats, scissors, forceps, and a variety of tools designed to grasp, hold, or manipulate abdominal organs and tissues. Improvements such as the disposable scalpel blade in the 1920s and disposable instruments in the 1970s have reduced labor costs of hospitals. The introduction of staplers for gastrointestinal side-to-side and end-to-end anastomoses by Russian investigators, brought to the United States and developed by Ravitch and Steichen\textsuperscript{18} in the 1960s, was a major advance.

Hemostasis was facilitated by the development of a diathermy machine for electrosurgical cutting and cautery by William T. Bovie and introduced into clinical use by Harvey Cushing at the Peter Bent Brigham Hospital in 1920, eliminating the need to clamp and ligate small vessels. Since then, topical preparations, clips, electrical energy, and ultrasonic energy have been incorporated into various devices that have enabled minimally invasive surgery.

**TECHNOLOGY DRIVES SURGERY**

Development of minimally invasive surgery was dependent on the visualization of organs in the abdominal cavity through a scope. In 1806, Phillipp Bozzini made a major contribution by constructing a “lichtleiter,” a scope that incorporated mirrors to reflect light back to the eye. It was used primarily for gynecologic examinations (Fig. 1-4). The development of small bulbs illuminated by electric current enabled laparoscopy for diagnosis beginning in the first half of the 20th century, and flexible fiberoptic scopes for examining the interior of the gastrointestinal tract followed in the 1950s.
Numerous advances in technology, many driven by the computer and the computer chip television camera, enabled laparoscopic surgery, which revolutionized abdominal surgery.

Laparoscopic surgery had its origin in obstetrics and gynecology, with the first laparoscopic organ removal, salpingectomy, performed by Tarasconi in 1975. This was followed by laparoscopic cholecystectomy, first performed by Muhe in Germany in 1985, by Mouret in France in 1987, and Reddick in the United States in 1988. Since then, every abdominal organ has been subjected to laparoscopic procedures.

The most recent technological development is the use of robots in surgery. After years of research and development by many organizations, the da Vinci surgery system was approved by the US Food and Drug Administration in 2000 for general laparoscopic surgery. The surgeon sits at a console where the interior of the abdomen is projected on a screen and uses a computer to control a robotic arm to which are attached various instruments. Newer versions, including a console for an assistant, have been used in general
surgery and the surgical specialties. The advantages and disadvantages of robotic surgery are still under evaluation as experience accumulates and the technology continues to improve.

**SUMMARY**

Early abdominal surgery was enabled by the discovery of general anesthesia, means to control or eliminate infection, and the evolution of the hospital, where patients could be housed and surgeons could work in a supportive environment that included nurses and hospital administrators. Later, development of the basic sciences enabled the development of new operations and methods to deal with altered physiology and body chemistry caused by illness, trauma, and complex surgical procedures. Most recently, striking advances in technology have enabled the development of minimally invasive and robotic surgery.

**REFERENCES**

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Surgeons of every specialty face increasingly complex surgical challenges. In addition, modern surgical treatment can be offered to more fragile patients, with successful outcomes. Mastery of the scientific fundamentals of perioperative management is required to achieve satisfactory results. The organ system–based approach presented here allows the surgeon to address the patient’s pre- and postoperative needs with a comprehensive surgical plan. This chapter will serve as a summary guide to best practices integral to conducting surgical procedures in the modern era.

**MANAGEMENT OF PAIN AND DELIRIUM**

The most common neuropsychiatric complications following abdominal surgery are pain and delirium. Moreover, uncontrolled pain and delirium prevent the patient from contributing to vital aspects of his or her care, such as ambulation and respiratory toilet, and promote an unsafe environment that may lead to the unwanted dislodgment of drains and other supportive
devices, with potentially life-threatening consequences. Pain and delirium usually coexist in the postoperative setting, and each can contribute to the development of the other. Despite high reported rates of overall patient satisfaction, pain control is frequently inadequate in the perioperative setting, with high rates of complications such as drowsiness from overtreatment and unacceptable levels of pain from undertreatment. Therefore, it is mandatory that the surgical plan for every patient include close monitoring of postoperative pain and delirium and regular assessment of the efficacy of pain control.

Pain management, like all surgical planning, begins in the preoperative assessment. In the modern era, a large proportion of surgical patients will require special attention with respect to pain control. Patients with preexisting pain syndromes, such as sciatica or interspinal disc disease, or patients with a history of opioid use may have a high tolerance for opioid analgesics. Every patient’s history should include a thorough investigation for chronic pain syndrome, addiction (active or in recovery), and adverse reactions to opioid, nonsteroidal, or epidural analgesia. The pain control strategy may include consultation with a pain control anesthesiology specialist, but it is the responsibility of the operating surgeon to identify complicated patients and construct an effective pain control plan.

**Opioid Analgesia**

Postoperative pain control using opioid medication has been in use for thousands of years. Hippocrates advocated the use of opium for pain control. The benefits of postoperative pain control are salutary and include improved mobility and respiratory function and earlier return to normal activities. The most effective strategy for pain control using opioid analgesia is patient-controlled analgesia (PCA), wherein the patient is instructed in the use of a preprogrammed intravenous pump that delivers measured doses of opioid (usually morphine or meperidine). In randomized trials, PCA has been shown to provide superior pain control and patient satisfaction compared to interval dosing, but PCA has not been shown to improve rates of pulmonary and cardiac complications or length of hospital stay, and there is evidence that PCA may contribute to postoperative ileus. In addition, PCA may be unsuitable for patients with a history of substance abuse, high opioid...
tolerance, or those with atypical reactions to opioids.

Regional Analgesia

Due to the limitations of PCA, pain control clinicians have turned to regional analgesia as an effective strategy for the management of postoperative pain. Postoperative epidural analgesia involves the insertion of a catheter into the epidural space of the lumbar or thoracic spine, enabling the delivery of local anesthetics or opioids directly to the nerve roots. The insertion procedure is generally safe, with complication rates of motor block and numbness between 0.5% and 7%, and an epidural abscess rate of 0.5 per thousand. Potential advantages of epidural analgesia include elimination of systemic opioids, and thus less respiratory depression, and improvement in pulmonary complications and perioperative ileus. There have been several large trials, a meta-analysis, and a systematic review comparing PCA with epidural analgesia in the setting of abdominal surgery. These studies indicate that epidural analgesia provides more complete analgesia than PCA throughout the postoperative course. Furthermore, in randomized prospective series of abdominal procedures, epidural analgesia has been associated with decreased rates of pulmonary complications and postoperative ileus. Epidural analgesia requires a skilled anesthesia clinician to insert and monitor the catheter and adjust the dosage of neuraxial medication. Some clinicians may prefer correction of coagulopathy before inserting or removing the catheter, although the American Society of Anesthesiologists (ASA) has not issued official guidelines on this issue.

Peripheral nerve blocks are also effective in perioperative pain control and do not carry the same potential morbidities as the epidural approach. Using ultrasound guidance, a skilled practitioner can deliver a long-acting local anesthetic into the transversus abdominis plane (TAP) or in the rectus sheath to establish analgesia both intraoperatively and postoperatively. Randomized clinical data have confirmed the efficacy of regional blocks in controlling pain and reducing use of opioid analgesia.

Analgesia with Nonsteroidal Anti-Inflammatory Drugs
Oral nonsteroidal anti-inflammatory drugs (NSAIDs) have long been used for postoperative analgesia in the outpatient setting and, with the development of parenteral preparations, have come into use in the inpatient population. This class of medication has no respiratory side effects and is not associated with addiction potential, altered mental status, or ileus. In addition, these medications provide effective pain relief in the surgical population. However, use of NSAIDs has not been universally adopted in abdominal surgery due to concerns regarding the platelet dysfunction and erosive gastritis associated with heavy NSAID use. In prospective trials, NSAIDs were found to provide effective pain control without bleeding or gastritis symptoms following laparoscopic cholecystectomy, abdominal hysterectomy, and inguinal hernia repair. NSAIDs have also been shown to improve pain control and decrease morphine dosage when used in combination following appendectomy.

The sensation of pain is very subjective and personal. Accordingly, the surgeon must individualize the pain control plan to fit the needs of each patient. The pain control modalities discussed above can be used in any combination, and the surgeon should not hesitate to use all resources at his or her command to provide adequate relief of postoperative pain.

Postoperative Delirium

Delirium, defined as acute cognitive dysfunction marked by fluctuating disorientation, sensory disturbance, and decreased attention, is an all too common complication of surgical procedures, with reported rates of 11% to 25%, with the highest rates reported in the elderly population. The postoperative phase of abdominal surgery exposes patients, some of whom may be quite vulnerable to delirium, to a large number of factors that may precipitate or exacerbate delirium (Table 2-1). These factors can augment one another: postoperative pain can lead to decreased mobility, causing respiratory compromise, atelectasis, and hypoxemia. Escalating doses of narcotics to treat pain can cause respiratory depression and respiratory acidosis. Hypoxemia and delirium can cause agitation, prompting treatment with benzodiazepines, further worsening respiratory function and delirium. This vicious cycle can result in serious complications or death. Preoperative recognition of high-risk patients and meticulous monitoring of every patient’s
mental status are the most effective ways to prevent postoperative delirium; treatment can be remarkably difficult once the cycle has begun.

**TABLE 2-1: CAUSES OF PERIOPERATIVE DELIRIUM**

- Pain
- Narcotic analgesics
- Sleep deprivation
- Hypoxemia
- Hyperglycemia
- Acidosis
- Withdrawal (alcohol, narcotics, benzodiazepines)
- Anemia
- Dehydration
- Electrolyte imbalance (sodium, potassium, magnesium, calcium, phosphate)
- Fever
- Hypotension
- Infection (pneumonia, incision site infection, urinary tract infection)
- Medication (antiemetics, antihistamines, sedatives, anesthetics)
- Postoperative myocardial infarction

Patient factors that are associated with high risk of perioperative delirium include age greater than 70 years, preexisting cognitive impairment or prior episode of delirium, history of alcohol or narcotic abuse, and malnutrition.\(^{22,25}\) Procedural factors associated with high delirium risk include operative time greater than 2 hours, prolonged use of restraints, presence of a urinary catheter, addition of more than 3 new medications, and reoperation.\(^{26}\)

Once the patient’s risk for postoperative delirium is identified, perioperative care should be planned carefully to decrease other controllable factors. Epidural analgesia has been associated with less delirium than PCA after abdominal surgery.\(^{26}\) Sedation or “sleepers” should be used judiciously, if at all, with high-risk patients. If the patient requires sedation, neuroleptics such as haloperidol and the atypical neuroleptics such as olanzapine are
tolerated much better than benzodiazepines.\textsuperscript{27} The patient’s mental status, including orientation and attention, should be assessed with every visit and care should be taken to avoid anemia, electrolyte imbalances, dehydration, and other contributing factors.

Once the diagnosis of postoperative delirium is established, it is important to recognize that some of the causes of delirium are potentially life-threatening, and immediate action is necessary. Evaluation begins with a thorough history and physical examination at the bedside by the surgeon. The history should focus on precipitating events such as falls (possible traumatic brain injury), recent procedures, use of opioids and sedatives, changes in existing medications (eg, withholding of thyroid replacement or antidepressants), and consideration of alcohol withdrawal. The vital signs and fluid balance may suggest sepsis, hypovolemia, anemia, or dehydration. The exam should include brief but complete sensory and motor neurologic examinations to differentiate delirium from stroke. Pay attention to common sites of infection such as the surgical wound, the lungs, and intravenous catheters. Urinary retention may be present as a result of medication or infection. Deep venous thrombosis may be clinically evident as limb swelling. Postoperative myocardial infarction (MI) may often present as acute cardiogenic shock.

The history and physical examination should then direct the use of lab tests. Most useful are the electrolytes, blood glucose, and complete blood cell count. Pulse oximetry and arterial blood gases may disclose hypercapnia or hypoxemia. Chest x-ray may disclose atelectasis, pneumonia, acute pulmonary edema, or pneumothorax. Cultures may be indicated in the setting of fever or leukocytosis, but will not help immediately. Electrocardiogram (ECG) and cardiac troponin may be used to diagnose postoperative MI.

Resuscitative measures may be required if life-threatening causes of delirium are suspected. Airway control, supplemental oxygen, and fluid volume expansion should be considered in patients with unstable vital signs. The patient should not be sent out of the monitored environment for further tests, such as head computed tomography (CT), until the vital signs are stable and the agitation is controlled. Treatment of postoperative delirium depends on treatment of the underlying causes. Once the underlying cause has been treated, delirium may persist, especially in elderly or critically ill patients, who regain orientation and sleep cycles slowly. In these patients, it is important to provide orienting communication and mental stimulation during
the day and to promote sleep during the night. The simplest ways are the most effective: contact with family members and friends, use of hearing aids, engagement in activities of daily living, and regular mealtimes. Sleep can be promoted by keeping the room dark and quiet throughout the evening and preventing unnecessary interruptions. If nighttime sedation is required, atypical neuroleptics or low-dose serotonin reuptake inhibitors such as trazodone are better tolerated than benzodiazepines. If agitation persists, escalating doses of neuroleptics (or benzodiazepines in the setting of alcohol withdrawal) can be used to control behavior, but underlying organic causes of delirium must be investigated.

**CARDIAC EVALUATION**

**Risk Assessment**

It has been estimated that 1 million patients have a perioperative MI each year, and the contribution to medical costs is $20 billion annually. Thoracic, upper abdominal, neurologic, and major orthopedic procedures are associated with increased cardiac risk. Diabetes, prior MI, unstable angina, and decompensated congestive heart failure (CHF) are most predictive of perioperative cardiac morbidity and mortality, and patients with these conditions undergoing major surgery warrant further evaluation (Table 2-2). Patient factors conferring intermediate risk include mild angina and chronic renal insufficiency with baseline creatinine ≥2 mg/dL. It is worth noting that women were underrepresented in the studies on which the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines are based. A retrospective study in gynecologic patients found that hypertension and previous MI were major predictors of postoperative cardiac events, as opposed to the ACC/AHA guidelines, which indicate that they are minor and intermediate criteria, respectively. Vascular surgical patients are at highest risk because of the prevalence of underlying coronary disease in this population. Other high-risk procedural factors include emergency surgery, long operative time, and high fluid replacement volume. Intraperitoneal procedures, carotid endarterectomy, thoracic surgery, head and neck procedures, and orthopedic procedures carry an intermediate
risk and are associated with a 1% to 5% risk of a perioperative cardiac event.\textsuperscript{30}

\textbf{TABLE 2-2: CLINICAL PREDICTORS OF INCREASED RISK FOR PERIOPERATIVE CARDIAC COMPLICATIONS}

\textbf{Major}
Recent myocardial infarction (within 30 days)
Unstable or severe angina
 Decompensated congestive heart failure
Significant arrhythmias (high-grade atrioventricular block, symptomatic ventricular arrhythmias with underlying heart disease, supraventricular arrhythmias with uncontrolled rate)
Severe valvular disease

\textbf{Intermediate}
Mild angina
Any prior myocardial infarction by history or electrocardiogram
Compensated or prior congestive heart failure
Diabetes mellitus
Renal insufficiency

\textbf{Minor}
Advanced age
Abnormal electrocardiogram
Rhythm other than sinus (eg, atrial fibrillation)
Poor functional capacity
History of stroke
Uncontrolled hypertension (eg, diastolic blood pressure >10 mm Hg)

Perioperative evaluation to identify patients at risk for cardiac complications is essential in minimizing morbidity and mortality. Workup should start with history, physical exam, and ECG to determine the existence of cardiac pathology. Screening with chest radiographs and ECG is required for men over 40 and women over 55. According to the ACC/AHA guidelines, initial preoperative cardiac risk can be assessed using a clinical calculator, the
Revised Cardiac Risk Index (RCRI).\textsuperscript{34} This index includes history of ischemic heart disease, CHF, cerebrovascular disease, diabetes, chronic kidney disease, and planned high-risk procedure. Advanced or invasive testing is reserved for patients with 2 or more of these risk factors. Overall functional ability is the best clinical measure of cardiac fitness. Patients who can exercise without limitations can generally tolerate the stress of major surgery.\textsuperscript{35} Limited exercise capacity may indicate poor cardiopulmonary reserve and the inability to withstand the stress of surgery. Poor functional status is the inability to perform activities such as driving, cooking, or walking less than 5 km/h.

Intraoperative risk factors include operative site, inappropriate use of vasopressors, and unintended hypotension. Intra-abdominal pressure exceeding 20 mm Hg during laparoscopy can decrease venous return from the lower extremities and thus contribute to decreased cardiac output,\textsuperscript{36} and Trendelenburg positioning can result in increased pressure on the diaphragm from the abdominal viscera, subsequently reducing vital capacity. Intraoperative hypertension has not been isolated as a risk factor for cardiac morbidity, but it is often associated with wide fluctuations in pressure and has been more closely associated with cardiac morbidity than intraoperative hypotension. Preoperative anxiety can contribute to hypertension even in normotensive patients. Patients with a history of hypertension, even medically controlled hypertension, are more likely to be hypertensive preoperatively. Those with poorly controlled hypertension are at greater risk of developing intraoperative ischemia, arrhythmias, and blood pressure derangements, particularly at induction and intubation. Twenty-five percent of patients will exhibit hypertension during laryngoscopy. Patients with chronic hypertension may not necessarily benefit from lower blood pressure during the preoperative period because they may depend on higher pressures for cerebral perfusion. Those receiving antihypertensive medications should continue them up until the time of surgery. Patients taking β-blockers are at risk of withdrawal and rebound ischemia. Key findings on physical examination include retinal vascular changes and an S\textsubscript{4} gallop consistent with left ventricular hypertrophy. Chest radiography may show an enlarged heart, also suggesting left ventricular hypertrophy.

ECG should be obtained in patients with chest pain, diabetes, prior revascularization, prior hospitalization for cardiac causes, all men age 45 or
older, and all women age 55 or older with 2 or more risk factors. High- or intermediate-risk patients should also have a screening ECG. A lower-than-normal ejection fraction demonstrated on echocardiography is associated with the greatest perioperative cardiac risk and should be obtained in all patients with symptoms suggesting heart failure or valvular disease. Tricuspid regurgitation indicates pulmonary hypertension and is often associated with sleep apnea. The chest x-ray is used to screen for cardiomegaly and pulmonary congestion, which may signify ventricular impairment.

Exercise testing demonstrates a propensity for ischemia and arrhythmias under conditions that increase myocardial oxygen consumption. Numerous studies have shown that performance during exercise testing is predictive of perioperative mortality in noncardiac surgery. ST-segment changes during exercise including horizontal depression greater than 2 mm, changes with low workload, and persistent changes after 5 minutes of exercise are seen in severe multivessel disease. Other findings include dysrhythmias at a low heart rate, an inability to raise the heart rate to 70% of predicted, and sustained decrease in systolic pressure during exercise.

Unfortunately, many patients are unable to achieve adequate workload in standard exercise testing because of osteoarthritis, low back pain, and pulmonary disease. In this case, pharmacologic testing is indicated with a dobutamine echocardiogram. Dobutamine is a β-agonist that increases myocardial oxygen demand and reveals impaired oxygen delivery in those with coronary disease. Echocardiography concurrently visualizes wall motion abnormalities due to ischemia. Transesophageal echocardiography may be preferable to transthoracic echocardiography in obese patients because of their body habitus and has been shown to have high negative predictive value in this group. Nuclear perfusion imaging with vasodilators such as adenosine or dipyridamole can identify coronary artery disease and demand ischemia. Heterogeneous perfusion after vasodilator administration demonstrates an inadequate response to stress. Wall motion abnormalities indicate ischemia, and an ejection fraction lower than 50% increases the risk of perioperative mortality. Angiography should only be performed if the patient may be a candidate for revascularization.

**Coronary Disease**

Most perioperative MIs are caused by plaque rupture in lesions that do not
produce ischemia during preoperative testing.\textsuperscript{38} This presents an obvious challenge for detecting patients at risk. Stress testing has a low positive predictive value in patients with no cardiac risk factors and has been associated with an unacceptably high rate of false-positive results.\textsuperscript{39}

Preoperative optimization may include medical management, percutaneous coronary interventions (PCIs), or coronary artery bypass grafting (CABG).\textsuperscript{40} The ACC/AHA guidelines\textsuperscript{29} recommend revascularization for patients whose preoperative testing reveals severe disease that warrants intervention according to practice guidelines for coronary artery disease, independent of their perioperative status.

Patients warranting emergent CABG will be at greatest risk for that procedure. A recent study from the Veterans Administration hospitals recommends against revascularization in patients with stable cardiac symptoms.\textsuperscript{41} Preoperative PCI does not decrease the risk of future MI or mortality in patients with stable coronary disease, and only targets stenotic lesions, rather than those most likely to rupture. One retrospective study found no reduction in morbidity or perioperative MI after percutaneous transluminal coronary angioplasty, and the authors proposed that surgery within 90 days of balloon angioplasty increased the risk of thrombosis.\textsuperscript{42} However, PCI done more than 90 days before surgery did provide benefit when compared to those who had no intervention at all. Another retrospective study found that patients who have surgery within 2 weeks of stenting had a high incidence of perioperative MI, major bleeding, or death.\textsuperscript{43} Although a retrospective review from the Coronary Artery Surgery Study registry showed a lower mortality rate in patients with coronary artery disease who were post-CABG than those without CABG (0.09\% vs 2.4\%), this benefit did not include the morbidity associated with CABG itself. Unfortunately, the benefit was overwhelmed by the 2.3\% morbidity rate seen with CABG in this cohort.\textsuperscript{44} Survival benefit of CABG over medical management is realized at 2 years or more after surgery,\textsuperscript{45} so preoperative mortality may decrease overall short-term survival. Revascularization and bypass grafting should be restricted to patients who would benefit from the procedure independent of their need for noncardiac surgery. One of the disadvantages of PCI in the preoperative setting is the need for anticoagulation to prevent early stent occlusion. The use of platelet inhibitors to prevent stent occlusion must be included in the overall risk assessment, especially for surgery of the central
nervous system.

Catecholamine surges can cause tachycardia, which may alter the tensile strength of coronary plaques and incite plaque rupture.\textsuperscript{46,47} Catecholamine surges can also increase blood pressure and contractility, contributing to platelet aggregation and thrombosis after plaque rupture and increasing the possibility of complete occlusion of the arterial lumen.\textsuperscript{48} Perioperative \(\beta\)-blockade mitigates these effects and has been shown to reduce MI and mortality from MI by over 30% in vascular surgical patients with reversible ischemia.\textsuperscript{46} Patients at highest risk still have a cardiac event rate of 10%, even with adequate perioperative \(\beta\)-blockade.\textsuperscript{29}

In 1998, a landmark study\textsuperscript{49} demonstrated a 55% reduction in mortality in noncardiac surgical patients with known coronary disease who were given atenolol perioperatively. This was followed by the DECREASE trial,\textsuperscript{50} which showed a 10-fold reduction in perioperative MI and death compared to placebo. Thereafter, perioperative \(\beta\)-blockade was widely adopted as a quality measure. However, additional later investigations have shown that although perioperative \(\beta\)-blockers benefit patients with known ischemia, low-risk patients may in fact be harmed.\textsuperscript{51} Tight rate control has been associated with increased risk of hypotension and bradycardia requiring intervention and stroke without any significant decrease in mortality.\textsuperscript{52-55} Furthermore, critical analysis of the literature shows that studies have been inconsistent in the type of medication administered, the duration and timing of administration, and the target for heart rate control.\textsuperscript{56} Consequently, results are difficult to interpret. Thus, prophylactic perioperative \(\beta\)-blockade should be restricted to patients with cardiac ischemia and has a limited role in patients with low or moderate risk of postoperative cardiac events.\textsuperscript{29}

**Congestive Heart Failure and Arrhythmia**

CHF is associated with coronary disease, valvular disease, ventricular dysfunction, and all types of cardiomyopathy. These are all independent risk factors that should be identified prior to surgery. Even compensated heart failure may be aggravated by fluid shifts associated with anesthesia and abdominal surgery and deserves serious consideration. Perioperative mortality increases with higher New York Heart Association class and preoperative pulmonary congestion. CHF should be treated to lower filling
pressures and improve cardiac output before elective surgery. β-Blockers, angiotensin-converting enzyme inhibitors, and diuretics can be employed to this end. The patient should be stable for 1 week before surgery.57

Arrhythmias and conduction abnormalities elicited in the history, on exam, or on ECG should prompt investigation into metabolic derangements, drug toxicities, or coronary disease. In the presence of symptoms or hemodynamic changes, the underlying condition should be reversed and then medication given to treat the arrhythmia. Indications for antiarrhythmic medication and cardiac pacemakers are the same as in the nonoperative setting. Nonsustained ventricular tachycardia and premature ventricular contractions have not been associated with increased perioperative risk and do not require further intervention.58,59

**Valvular Disease**

Valvular disease should be considered in patients with symptoms of CHF, syncope, and a history of rheumatic heart disease. Aortic stenosis (AS) is a fixed obstruction to the left ventricular outflow tract, limiting cardiac reserve and an appropriate response to stress. History should elicit symptoms of dyspnea, angina, and syncope; examination may reveal a soft S₂, a late-peaking murmur, or a right-sided crescendo–decrrescendo murmur radiating to the carotids. AS is usually caused by progressive calcification or congenital bicuspid valve. Critical stenosis exists when the valve area is less than 0.7 cm² or transvalvular gradients are greater than 50 mm Hg and is associated with an inability to increase cardiac output with demand. If uncorrected, AS is associated with a 13% risk of perioperative death. Valve replacement is indicated prior to elective surgery in patients with symptomatic stenosis.29 Myocardial ischemia may occur in the absence of significant coronary artery occlusion in the presence of aortic valve disease. Perioperative management should include optimizing the heart rate to between 60 and 90 beats per minute and avoiding atrial fibrillation if possible. Because of the outflow obstruction, stroke volume may be fixed and bradycardia will lower cardiac output. Similarly, hypotension is also poorly tolerated.

Aortic regurgitation (AR) is associated with backward flow into the left ventricle during diastole and reduced forward stroke volume. Bradycardia
facilitates regurgitation by increased diastolic time. Chronic AR causes massive left ventricular dilatation (cor bovinum) and hypertrophy, which is associated with decreased left ventricular function at later stages. AR is most often caused by rheumatic disease or congenital bicuspid valve. Medical treatment includes rate control and afterload reduction. Without valve replacement, survival is approximately 5 years once patients become symptomatic. This is an obvious consideration when planning any other surgical procedures.

Tricuspid regurgitation is usually caused by pulmonary hypertension secondary to severe left-sided failure. Other causes include endocarditis, carcinoid syndrome, and primary pulmonary hypertension. Hypovolemia, hypoxia, and acidosis can increase right ventricular afterload and should be avoided in the perioperative period.

Mitral stenosis is an inflow obstruction that prevents adequate left ventricular filling. The transvalvular pressure gradient depends on atrial kick, heart rate, and diastolic filling time. Tachycardia decreases filling time and contributes to pulmonary congestion. Mitral regurgitation is also associated with pulmonary hypertension with congestion, as the pathologic valve prevents forward flow, causing left atrial dilatation and subsequent atrial arrhythmias. History and physical exam should focus on signs of CHF such as orthopnea, pedal edema, dyspnea, reduced exercise tolerance, and auscultatory findings such as murmurs and an S₃ gallop. Neurologic deficits may signify embolic sequelae of valve disease. Perioperative rate control is essential for maintaining adequate cardiac output. ECG findings will reflect related arrhythmias and medications but will not be specific for valve disease. Laboratory studies should identify secondary hepatic dysfunction or pulmonary compromise. Left ventricular hypertrophy is an adaptive response, which may cause subsequent pulmonary hypertension and diastolic dysfunction.

Prosthetics in the mitral position pose the greatest risk for thromboembolism, and the risk increases with valve area and low flow. Mechanical valves pose a higher risk than tissue valves in patients with a history of valve replacement. Diuretics and afterload-reducing agents will enhance forward flow and minimize cardiopulmonary congestion. Patients with mitral valve prolapse (MVP) should receive antibiotics.

Mitral regurgitation may also impair left ventricular function and lead to pulmonary hypertension. Stroke volume is reduced by backward flow into the
atrium during systole. The left ventricle dilates to handle increasing end-
systolic volume, eventually causing concentric hypertrophy and decreased
contractility. The end result may be decreased ejection fraction and CHF. A
decrease in systemic vascular resistance and increase in atrial contribution to
the ejection fraction can both improve forward flow and reduce the amount of
regurgitation. Echocardiography can clarify the degree of valvular
impairment. Medical treatment centers on afterload reduction with
vasodilators and diuretics. MVP is present in up to 15% of women and is
usually associated with a midsystolic click and late systolic murmur on
physical exam. Murmur is indicative of prolapse. Although MVP is
associated with connective tissue disorders, it usually occurs in otherwise
healthy, asymptomatic patients. Echocardiography is used to confirm the
diagnosis and evaluate the degree of prolapse. Chronically, MVP may be
associated with mitral regurgitation, emboli, and increased risk of
endocarditis. Prolapse may be aggravated by decreased preload, which should
be minimized in the perioperative period. Patients with MVP are at risk of
ventricular arrhythmias with sympathetic stimulation and endocarditis, which
can be addressed with pain control and antibiotic prophylaxis, respectively.

Individuals with underlying structural cardiac defects are at increased risk
for developing endocarditis after invasive procedures. Surgical procedures
involving mucosal surfaces or infected tissues may cause transient bacteremia
that is usually short-lived. Certain procedures are associated with a greater
risk of endocarditis and warrant prophylaxis (Table 2-3). Abnormal valves,
endocardium, or endothelium can harbor the bloodborne bacteria for a longer
period of time, and infection and inflammation can ensue. Although there are
no randomized trials regarding endocarditis prophylaxis, the AHA
recommends prophylaxis for those at high and moderate risk for developing
the condition. The highest-risk patients have prosthetic heart valves, cyanotic
congenital heart disease, or a history of endocarditis (even without structural
abnormality). Conditions associated with moderate risk include congenital
septal defects, patent ductus arteriosus, coarctation of the aorta, and bicuspid
aortic valve. Hypertrophic cardiomyopathy and acquired valvular disease also
fall into this category. MVP is a prevalent and often situational condition.
Normal valves may prolapse in the event of tachycardia or hypovolemia and
may reflect normal growth patterns in young people. Prolapse without leak or
regurgitation seen on Doppler studies is not associated with risk greater than
that of the general population, and no antibiotic prophylaxis is necessary.
However, the jet caused by the prolapsed valve increases the risk of bacterial adherence and subsequent endocarditis. Leaky valves detected by physical exam or Doppler warrant consideration for prophylactic antibiotics. Patients with significant regurgitation are more likely to be older and men, and other studies have shown that older men are more likely to develop endocarditis. Some advocate prophylaxis for men older than 45 years with MVP even in the absence of audible regurgitation. Prolapse secondary to myxomatous valve degeneration also warrants prophylactic antibiotics.

### TABLE 2-3: AHA ENDOCARDITIS PROPHYLAXIS RECOMMENDATIONS

**Antibiotic Coverage Recommended**
- Respiratory: tonsillectomy/adenoidectomy; bronchoscopy with biopsy; procedures involving respiratory mucosa
- Gastrointestinal tract: any procedure in the setting of infected tissue in the gastrointestinal tract
- Genitourinary tract: any procedure in the setting of established infection

**Antibiotic Coverage Not Recommended**
- Respiratory: endotracheal intubation; bronchoscopy without biopsy; tympanostomy
- Gastrointestinal tract: transesophageal echocardiography; endoscopy without biopsy
- In uninfected tissue: urethral catheterization; uterine dilation and curettage; therapeutic abortion; manipulation of intrauterine devices
- Other: cardiac catheterization; pacemaker placement; circumcision; incision or biopsy on prepped skin

For patients at risk, the goal should be administration of antibiotics in time to attain adequate serum levels during and after the procedure. For most operations, a single intravenous dose given 1 hour prior to incision will achieve this goal. Antibiotics should generally not be continued for more than 6 to 8 hours after the procedure to minimize the chance of bacterial resistance. In the case of oral, upper respiratory, and esophageal procedures, α-hemolytic *Streptococcus* is the most common cause of endocarditis, and
Antibiotics should be targeted accordingly. Oral amoxicillin, parenteral ampicillin, and clindamycin for penicillin-allergic patients are suitable medications. Erythromycin is no longer recommended for penicillin-allergic patients because of gastrointestinal side effects and variable absorption. Antibiotics given to those having genitourinary and nonesophageal gastrointestinal procedures should target enterococci. While gram-negative bacteremia can occur, it rarely causes endocarditis. Parenteral ampicillin and gentamicin are recommended for highest-risk patients. Moderate-risk patients may receive amoxicillin or ampicillin. Vancomycin may be substituted in patients allergic to penicillin.

PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC MEDICATION

Estimates suggest that 250,000 patients receiving chronic anticoagulation require surgery in the United States each year. Operative bleeding risk must be balanced against thromboembolic risk for the patient off of anticoagulation and requires careful judgment. Factors that influence the risk of thromboembolism include the condition requiring chronic anticoagulation, the duration of the procedure, time expected off of anticoagulation, and the duration of perioperative immobility. Thromboembolic risk increases with the amount of time that the patient’s anticoagulation is subtherapeutic.

Primary indications for chronic anticoagulation include arterial embolism associated with mechanical valves and atrial fibrillation and venous thromboembolism (VTE). Arterial events precipitate stroke, and valvular and atrial clot and systemic emboli are higher risk for morbidity and mortality than venous events. Patients at highest risk for perioperative embolism include those with mechanical prosthetic mitral valves, aortic caged-ball and tilted valves, rheumatic heart disease, or history of stroke or transient ischemic attacks (TIAs) in the past 3 months. The risk of thromboembolism without anticoagulation is higher than 10% per year in these high-risk patients.

Patients at moderate risk of thromboembolism without anticoagulation (4%-10% per year) have atrial fibrillation, a bileaflet valve, or history of stroke or TIA. The CHADS2 score (CHF, hypertension, age, diabetes, and stroke) further stratifies embolic risk for patients with atrial fibrillation based
on comorbidities. One point is assigned for hypertension, diabetes, CHF, and age >75 years; 2 points are assigned for history of stroke or TIA. Patients with a cumulative score of 5 to 6 are highest risk; those with a score of 3 to 4 are moderate risk; and those with a score of 0 to 2 without history of stroke or TIA are low risk.

Chronic anticoagulation is indicated for VTE. Patients with VTE within 3 months of surgery and severe thrombophilia are at highest risk for perioperative events and should receive bridging anticoagulation with therapeutic doses of low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin (UFH). Patients at moderate risk include those with a thromboembolic event 3 to 12 months before surgery and less severe thrombophilias. They can receive therapeutic or subtherapeutic doses of anticoagulation depending on the risk of bleeding associated with the procedure. Patients with a remote event are at lowest risk and do not require bridging anticoagulation. It is generally recommended to stop warfarin 5 days prior to surgery if a normal international normalized ratio (INR) is desired. Vitamin K may be administered in the days leading up to the event if the INR is not correcting quickly enough.

LMWH should be held 24 hours before surgery, and intravenous UFH should be held 4 hours before surgery. Oral anticoagulants may be started 12 to 24 hours postoperatively because they take at least 48 hours to affect coagulation. The timing of resuming intravenous and subcutaneous anticoagulants should be determined on a case-by-case basis.

Low-risk patients receiving clopidogrel or aspirin should have it held 5 to 10 days before surgery. Patients with coronary stents are chronically treated with clopidogrel and aspirin to mitigate the risk of stent thrombosis. Interruptions in therapy are associated with high risk of thrombosis and infarct. Patients with bare metal stents placed within 6 weeks of surgery or drug-eluting stents placed within 12 months of surgery should continue clopidogrel and aspirin in the perioperative period.

The perioperative antithrombotic guidelines from the American College of Chest Physicians are summarized in Table 2-4.

| TABLE 2-4: GUIDELINES FOR PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC MEDICATIONS |
PULMONARY EVALUATION

Pulmonary complications are common after surgery and can prolong hospital stays for 1 to 2 weeks. Complications include atelectasis, pneumonia, exacerbations of chronic pulmonary disorders, and respiratory failure requiring mechanical ventilation. Smoking, underlying chronic obstructive pulmonary disease (COPD), and poor exercise tolerance are the greatest risk factors for postoperative pulmonary complications. Physicians should ask about a history of smoking, decreased exercise capacity, dyspnea, and chronic cough. Examination should note pursed lip breathing, clubbing, and chest wall anatomy that could impair pulmonary function. Pulmonary testing is unnecessary in patients without a clear history of smoking or pulmonary disease. The predictive value of screening spirometry is unclear, and no threshold value has been identified to guide surgical decision-making. Forced expiratory volume in 1 second less than 50% of predicted is indicative of exertional dyspnea and may herald the need for further testing. Preoperative chest x-ray abnormalities are associated with postoperative pulmonary complications, but to this point, there are no recommendations for screening radiographs in patients without pulmonary disease. Any

<table>
<thead>
<tr>
<th>Complication</th>
<th>Standard Anticoagulation</th>
<th>Antiplatelet Therapy</th>
<th>Should Warfarin or Antiplatelet Therapy Be Stopped Preoperatively?</th>
<th>Is Bridging Anticoagulation Indicated?</th>
<th>When Should Anticoagulant or Antithrombotic Be Restarted Postoperatively?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk atrial fibrillation</td>
<td>Warfarin goal INR 2.0</td>
<td>None</td>
<td>Yes, 5 days</td>
<td>No</td>
<td>When taking oral</td>
</tr>
<tr>
<td>Moderate/high-risk atrial fibrillation</td>
<td>Warfarin goal INR 2.0</td>
<td>None</td>
<td>Yes, 5 days</td>
<td>No</td>
<td>When taking oral</td>
</tr>
<tr>
<td>Mechanical mitral valve</td>
<td>Warfarin goal INR 2.5-3.0</td>
<td>None</td>
<td>Yes, 5 days</td>
<td>Yes</td>
<td>Low bleeding risk: 24 hours, High bleeding risk: 48-72 hours</td>
</tr>
<tr>
<td>Mechanical aortic valve</td>
<td>Warfarin goal INR 2.0</td>
<td>None</td>
<td>Yes, 5 days</td>
<td>Yes</td>
<td>Low bleeding risk: 24 hours, High bleeding risk: 48-72 hours</td>
</tr>
<tr>
<td>Coronary stent</td>
<td>None</td>
<td>Clopidogrel</td>
<td>Yes, 5-10 days</td>
<td>No</td>
<td>Low bleeding risk: 24 hours, High bleeding risk: 48-72 hours</td>
</tr>
<tr>
<td>Bare metal coronary stent within 6 weeks</td>
<td>None</td>
<td>Aspirin and clopidogrel</td>
<td>No</td>
<td>No</td>
<td>Low bleeding risk: 24 hours, High bleeding risk: 48-72 hours</td>
</tr>
<tr>
<td>Drug-eluting stent within 12 months</td>
<td>None</td>
<td>Aspirin and clopidogrel</td>
<td>No</td>
<td>No</td>
<td>Low bleeding risk: 24 hours, High bleeding risk: 48-72 hours</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>Warfarin goal INR 2.0 for at least 3 months</td>
<td>No</td>
<td>Yes, 5-7 days</td>
<td>Low risk- no</td>
<td>Moderate- high risk- yes</td>
</tr>
</tbody>
</table>

Low risk: venous thromboembolism (VTE) >12 months ago, CHADS2 score 0-2, prior stroke or transient ischemic attack (TIA).
Moderate risk: VTE in past 3-12 months, moderate thrombophilia, recurrent VTE, cancer, CHADS2 score 3-4.
High risk: VTE in past 3 months, prior postoperative VTE, severe thrombophilia, CHADS2 score 5-6, rheumatic heart disease, or stroke or TIA within 3 months.

Abbreviation: INR, international normalized ratio.

preoperative chest x-ray must be examined for signs of hyperinflation consistent with COPD. While compensated hypercapnia has not been shown to be an independent predictor for postoperative ventilatory insufficiency in patients undergoing lung resection, preoperative arterial blood gas analysis provides useful baseline information for perioperative management of patients with chronic carbon dioxide retention. Transverse and upper abdominal incisions are associated with a higher rate of postoperative pulmonary complications than longitudinal midline incisions and lower abdominal incisions. Surgery longer than 3 hours is also associated with higher risk. General anesthesia is also associated with a higher risk of pulmonary complications than spinal, epidural, or regional anesthesia.

Physiologic changes can be seen in the postoperative period, especially after thoracic and upper abdominal procedures. Vital capacity may decrease by 50% to 60%, and is accompanied by an increased respiratory rate to maintain tidal volumes. Normally, functional residual capacity usually exceeds the closing capacity of the alveoli so they remain open throughout the respiratory cycle. Prolonged effects of anesthetics and narcotics reduce functional reserve capacity postoperatively, causing alveolar collapse. These changes can last for weeks to months. A distended abdomen can impair diaphragmatic excursion; painful incisions around the diaphragm and other respiratory muscles contribute to splinting and inadequate pulmonary toilet. Narcotics can inhibit sighing and coughing reflexes, which normally prevent alveolar collapse during periods of sleep and recumbency. Analgesics must be titrated carefully to permit deep breathing and avoid impairing respiratory effort.

Inspired nonhumidified oxygen and halogenated anesthetics are cytotoxic and interfere with surfactant production and mucociliary clearance. Depressed respiratory reflexes, diaphragm dysfunction, and decreased functional reserve capacity all contribute to alveolar collapse and pooling of secretions. Aspiration risk is also increased. Excess secretions cause further alveolar collapse and create a milieu ripe for bacterial infection and pneumonia. Intubated patients should receive antacid prophylaxis and gastric drainage to minimize the risk of aspiration.

Multiple analyses have found that poor exercise tolerance is the greatest predictor of postoperative pulmonary impairment. The ASA risk classification is a gauge of general status and is highly predictive of both
cardiac and pulmonary complications.\textsuperscript{75,76} Although advanced age is associated with increased incidence of chronic pulmonary disease and underlying impairment, it is not an independent risk factor for pulmonary complications.

Clearly, all smokers should be urged to stop before surgery. Even in the absence of coexisting pulmonary disease, smoking increases the risk of perioperative complications. Smoking confers a relative risk of 1.4 to 4.3, but a reduced risk of pulmonary complications has been shown in patients who stop smoking at least 8 weeks before cardiac surgery.\textsuperscript{77} Even 48 hours of abstinence can improve mucociliary clearance, decrease carboxyhemoglobin levels to those of nonsmokers, and reduce the cardiovascular effects of nicotine. A nicotine patch may help some patients with postoperative nicotine withdrawal but may not be advisable in patients at risk for poor wound healing.

COPD confers a relative risk of 2.7 to 4.7 in various studies. Symptoms of bronchospasm and obstruction should be addressed before surgery, and elective procedures should be deferred in patients having an acute exacerbation. Preoperative treatment may include bronchodilators, antibiotics, steroids, and physical therapy to increase exercise capacity. Patients with active pulmonary infections should have surgery delayed if possible. Asthmatics should have peak flow equivalent to their personal best or 80\% of predicted and should be medically optimized to achieve this goal. Pulse corticosteroids may be used without an increased risk of postoperative infection or other complication.\textsuperscript{78,79}

Malnourished patients may not be able to meet the demands of the increased work of breathing, increasing their risk for respiratory failure. Obese patients have higher rates of oxygen consumption and carbon dioxide production, which increases their work of breathing. They may also exhibit restrictive physiology due to a large, stiff chest wall. A complete history should inquire about sleeping difficulty and snoring. Obesity increases the amount of soft tissue in the oropharynx, which can cause upper airway obstruction during sleep. Fifty-five percent of morbidly obese patients may have sleep-related breathing disorders such as obstructive sleep apnea and obesity-hypoventilation syndrome.\textsuperscript{80} Symptoms include snoring and daytime sleepiness, and formal sleep studies are employed for definitive diagnosis. Sleep-disordered breathing is associated with hypoxia, hypercapnia, changes
in blood pressure, nocturnal angina, and increased cardiac morbidity and mortality including stroke and sudden death.\textsuperscript{81} Arterial blood gas with partial arterial oxygen pressure less than 55 mm Hg or partial arterial carbon dioxide pressure greater than 47 mm Hg confirms the diagnosis. An increased incidence of pulmonary hypertension and right-sided heart failure is seen in patients with obesity hypoventilation syndrome, and these patients should have an echocardiogram before surgery. In severe cases, intraoperative monitoring with a pulmonary artery catheter may be prudent.

In the patient who is awake, postoperative care should include coughing and deep breathing exercises, and in nonambulatory patients, early mobilization should include turning every 2 hours. Early ambulation prevents atelectasis and pooling of secretions and increases the ventilatory drive. Upright position distributes blood flow and minimizes shunting. Preoperative medications should be resumed expeditiously. Incentive spirometry and pulmonary toilet are pulmonary expansion maneuvers, which reduce the relative risk of pulmonary complications by 50\%\textsuperscript{81}. Patients should receive preoperative education about these techniques. Inhaled ipratropium and β-agonists, used together, may prevent postoperative wheezing and bronchospasm and should be prescribed in patients at risk. Intermittent positive-pressure ventilation and nasal bilevel positive airway pressure may be enlisted for secondary prevention. Epidural analgesia is superior to parenteral narcotics in abdominal and thoracic procedures for preventing pulmonary complications.

**GASTROINTESTINAL EVALUATION**

Stress ulceration has been a well-recognized complication of surgery and trauma since 1932, when Cushing reported gastric bleeding accompanying head injury. With later research in gastric physiology and shock, it has been recognized that the appearance of gastric erosion results from failure of the protective function of gastric mucosa and back diffusion of hydrogen ion, enabling gastric acid to injure the mucosa. Once the mucosa is injured, the defenses are further weakened, leading to further injury in a vicious cycle. The protective functions of the mucosa rely on the stomach’s rich blood flow to maintain high oxygen saturation. The most critical factor in the development of erosive ulceration now appears to be mucosal ischemia. Once
the rich blood supply of the mucosa is compromised, the protective mechanisms are impaired, and gastric acid causes erosion, bleeding, and perforation.

In the late 1970s, the incidence of gastric bleeding in critically ill patients was 15%. Recognition of the importance of organ perfusion has resulted in decreased rates of erosive stress gastritis. Factors often cited for this observation are improvement in resuscitation and monitoring technology, nutritional support, and effective agents for medical prophylaxis. The prophylactic medicines are targeted to reduce gastric acid secretion. Antacids have been shown to provide effective protection against erosive ulceration; however, there is increased risk of aspiration pneumonia. Antagonists of the histamine-2 (H₂) receptors of the parietal cells impair gastric acid secretion and are effective prophylaxis for erosive ulceration.

With the emergence of proton pump inhibitor (PPI) medications, more effective control of gastric acid secretion was available, leading to widespread use of PPIs for stress ulcer prophylaxis. In high-risk, critically ill patients, PPIs have been shown to decrease the incidence of gastrointestinal bleeding as compared to H₂ blockers, but both carry increased risk of ventilator-associated pneumonia and pseudomembranous colitis.

In the setting of elective operations when the patients are not critically ill, the incidence of stress ulceration is now very low, and routine use of ulcer prophylaxis medication has been questioned. In addition, the routine use of antisecretory medication, in particular in the elective setting, may lead to increased risk of pneumonia and pseudomembranous colitis.

**Postoperative Ileus**

Ileus is a condition of generalized bowel dysmotility that frequently impairs feeding in the postoperative setting. Ileus typically occurs after abdominal surgery, even if the bowel itself is not altered. It has been shown that laparotomy alone, without intestinal manipulation, leads to impaired gastrointestinal motility. The small bowel is typically affected the least and can maintain organized peristaltic contractions throughout the perioperative period. The stomach usually regains a normal pattern of emptying in 24 hours, and the colon is last to regain motility, usually in 48 to 72 hours.

The exact mechanism that causes postoperative ileus is not known;
however, physiologic studies have demonstrated the significant contribution of both inhibitory neural reflexes and local mediators within the intestinal wall. Inhibitory neural reflexes have been shown to be present within the neural plexuses of the intestinal wall itself and in the reflex arcs traveling back and forth from the intestine to the spinal cord. These neural pathways may account for the development of ileus during laparotomy without bowel manipulation. In addition, inflammatory mediators such as nitric oxide are present in manipulated bowel and in peritonitis and may play a role in development of ileus.

Ileus can be recognized from clinical signs, such as abdominal distension, nausea, and the absence of bowel sounds and flatus, which should prompt the diagnosis. Abdominal x-ray imaging typically shows dilated loops of small bowel and colon. Bowel obstruction must also be considered with these clinical findings, however, and CT or other contrast imaging may be required to rule out obstruction.

Ileus can also appear following nonabdominal surgery and can result from effects of medications (most often narcotics), electrolyte abnormalities (especially hypokalemia), and a wide variety of other factors.

Occasionally, the patient sustains a prolonged period of postoperative ileus. This can be due to a large number of contributing factors, such as intra-abdominal infection, hematoma, effects of narcotics and other medications, electrolyte abnormalities, and pain. In addition, there can be prolonged dysmotility from certain bowel operations, such as intestinal bypass.

The role of laparoscopic surgery in prevention of ileus is controversial. In theory, with less handling of the bowel laparoscopically and with smaller incisions, there should be less stimulation of the local mediators and neural reflexes. Animal studies comparing open and laparoscopic colon surgery indicate earlier resumption of normal motility studies and bowel movements with the laparoscopic approach. Human trials have not been conclusive. Several series demonstrate earlier tolerance of postoperative feeding with the laparoscopic approach to colon resection; however, these have been criticized for selection bias, and such studies are impossible to conduct in a blinded fashion.

Early mobilization has long been held to be useful in prevention of postoperative ileus. While standing and walking in the early postoperative period have been proven to have major benefits in pulmonary function and prevention of pneumonia, mobilization has no demonstrable effect on
In the expected course of uncomplicated abdominal surgery, the stomach is frequently drained by a nasogastric tube for the first 24 hours after surgery, and the patient is not allowed oral intake until there is evidence that colonic motility has returned, usually best evidenced by the passage of flatus. Earlier feeding and no gastric drainage after bowel surgery can be attempted for healthy patients undergoing elective abdominal surgery and has a high rate of success provided clinical symptoms of ileus are not present. In such patients, the use of effective preventive strategies is highly effective. These include maintenance of normal serum electrolytes, use of epidural analgesia, and avoidance of complications such as infection and bleeding. The routine use of nasogastric tubes for drainage in the postoperative period after abdominal surgery has come into question since the mid-1990s.

The most effective strategy for management of postoperative ileus following abdominal surgery has been the development of epidural analgesia. Randomized trials have shown that the use of nonnarcotic (local anesthetic–based) epidural analgesia at the thoracic level in the postoperative period results in a decreased period of postoperative ileus in elective abdominal surgery. Ileus reduction is not seen in lumbar-level epidural analgesia, suggesting that inhibitory reflex arcs involving the thoracic spinal cord may play a major role in postoperative ileus.

Narcotic analgesia, while effective for postoperative pain, has been shown to lengthen the duration of postoperative ileus, especially when used as a continuous infusion or as PCA. Patients report better control of postoperative pain with continuous infusion or PCA as compared to intermittent parenteral dosing. Many studies have been done comparing various types of opioid analgesics, in attempts to find a type that does not prolong ileus. There has been no clearly superior drug identified; all currently available opioids cause ileus. Opioid antagonists such as naloxone have been used in trials to decrease ileus in chronic narcotic use, and there is evidence that antagonists are effective in that setting; however, in postoperative ileus, the antagonists have not been shown to be clinically useful, again suggesting that other mechanisms are contributing to postoperative ileus.

**Early Postoperative Bowel Obstruction**

Early postoperative bowel obstruction refers to mechanical bowel
obstruction, primarily involving the small bowel, which occurs in the first 30 days following abdominal surgery. The clinical picture may frequently be mistaken for ileus, and these conditions can overlap. The clinical presentation of early postoperative bowel obstruction is similar to that of bowel obstruction arising de novo: crampy abdominal pain, vomiting, abdominal distention, and obstipation. The incidence of early postoperative bowel obstruction has been variable in published series, due to difficulty in differentiating ileus from early postoperative bowel obstruction, but the reported range is from 0.7% to 9.5% of abdominal operations.

Retrospective large series show that about 90% of early postoperative bowel obstruction is caused by inflammatory adhesions. These occur as a result of injury to the surfaces of the bowel and peritoneum during surgical manipulation. The injury prompts the release of inflammatory mediators that lead to formation of fibrinous adhesions between the serosal and peritoneal surfaces. As the inflammatory mediators are cleared and the injury subsides, these adhesions eventually mature into fibrous, firm, bandlike structures. In the early postoperative period, the adhesions are in their inflammatory, fibrinous form and, as such, do not usually cause complete mechanical obstruction.

Internal hernia is the next most common cause of early postoperative bowel obstruction and can be diagnosed with a CT scan but may not be recognized until laparotomy. Internal hernia occurs when gaps or defects are left in the mesentery or omentum or blind gutters or sacs are left in place during abdominal surgery. The typical scenario is colon resection involving extensive resection of the mesentery for lymph node clearance. If the resulting gap in the mesentery is not securely closed, small bowel loops may go through the opening and not be able to slide back out. A blind gutter may be constructed inadvertently during the creation of a colostomy. When the colostomy is brought up to the anterior abdominal wall, there is a space between the colon and the lateral abdominal wall, which may also trap the mobile loops of small bowel. Defects in the closure of the fascia during open or laparoscopic surgery can cause obstruction from incarcerated early postoperative abdominal wall hernia. Fortunately, internal hernia is a rare occurrence in the early postoperative period; however, it must be suspected in cases in which bowel anastomoses or colostomies have been constructed. Unlike adhesive obstruction, internal hernia requires operative intervention due to the high potential for complete obstruction and strangulation of the
Intussusception is a rare cause of early postoperative bowel obstruction in adults but occurs more frequently in children. Intussusception occurs when peristalsis carries a segment of the bowel (called the lead point) up inside the distal bowel like a rolled up stocking. The lead point is usually abnormal in some way and typically has some intraluminal mass, such as a tumor or the stump of an appendix after appendectomy. Other rare causes for early postoperative bowel obstruction include missed causes of primary obstruction at the index laparotomy, peritoneal carcinomatosis, obstructing hematoma, and ischemic stricture.

Management of early postoperative bowel obstruction depends on differentiation of adhesive bowel obstruction (the majority) from internal hernia and the other causes and from ileus. Clinicians generally rely on radiographic imaging to discern ileus from obstruction. For many years, plain x-ray of the abdomen was used: if the abdominal plain film showed air-distended loops of bowel and air-fluid levels on upright views, the diagnosis of obstruction was favored. However, plain radiographs can be misleading in the postoperative setting, and the overlap of ileus and obstruction can be confusing. Upper gastrointestinal contrast studies using a water-soluble agent have better accuracy, and abdominal CT using oral contrast has been shown to have 100% sensitivity and specificity in differentiating early postoperative bowel obstruction from postoperative ileus. However, unlike late adhesive bowel obstruction, contrast passage into the colon has not been shown to predict success for nonoperative management.

Once the diagnosis is made, management is tailored to the specific needs of the patient. Decompression via nasogastric tube is usually indicated, and ileus can be treated as discussed. Adhesive bowel obstruction warrants a period of expectant management and supportive care, as the majority of these problems will resolve spontaneously. Most surgical texts recommend that the waiting period can be extended to 14 days. If the early bowel obstruction lasts longer than 14 days, less than 10% resolve spontaneously, and exploratory laparotomy is indicated. The uncommon causes of early postoperative bowel obstruction, such as internal hernia, require more early surgical correction and should be suspected in the setting of complete obstipation, or when abdominal CT suggests internal hernia or complete bowel obstruction.
Renal Evaluation

Patients without a clinical history suggesting renal disease have a low incidence of significant electrolyte disturbances on routine preoperative screening. However, patients with renal or cardiac disease who are taking digitalis or diuretics or those with ongoing fluid losses (ie, diarrhea, vomiting, fistula, and bleeding) do have an increased risk of significant abnormalities and should have electrolytes measured and replaced preoperatively.

Preoperative urinalysis can be a useful screen for renal disease. Proteinuria marks intrinsic renal disease or CHF. Urinary glucose and ketones are suggestive of diabetes and starvation in the ketotic state, respectively. In the absence of recent genitourinary instrumentation, microscopic hematuria suggests calculi, vascular disease, or infection. A few leukocytes may be normal in female patients, but an increased number signifies infection. Epithelial cells are present in poorly collected specimens.

Patients with renal insufficiency or end-stage renal disease often have comorbidities that increase their overall risk in the perioperative period. Hypertension and diabetes correlate with increased risk of coronary artery disease and postoperative MI, impaired wound healing, wound infection, platelet dysfunction, and bleeding. Preoperative history should note the etiology of renal impairment, preoperative weight as a marker of volume status, and timing of last dialysis and the amount of fluid removed routinely. Evaluation should include a cardiac risk assessment. Physical exam should focus on signs of volume overload such as jugular venous distention and pulmonary crackles. In patients with clinically evident renal insufficiency, a full electrolyte panel (calcium, phosphorus, magnesium, sodium, and potassium) should be checked preoperatively, along with blood urea nitrogen and creatinine levels. Progressive renal failure is associated with catabolism and anorexia. Such patients need aggressive nutritional support during the perioperative periods to minimize the risk of infection and poor healing.

Dialysis-dependent patients should have dialysis within 24 hours before surgery and may benefit from monitoring of intravascular volume status during surgery. Blood samples obtained immediately after dialysis, before equilibration occurs, should only be used in comparison to predialysis values to determine the efficacy of dialysis.
Postoperatively, patients with chronic renal insufficiency or end-stage renal disease will need to have surgical volume losses replaced, but care should be taken to avoid excess. Replacement fluids should not contain potassium, and early dialysis should be employed to address volume overload and electrolyte derangements. Patients with impaired creatinine clearance should have their medications adjusted accordingly. For example, meperidine should be avoided because its metabolites accumulate in renal impairment and can lead to seizures.

The choice of postoperative fluid therapy depends on the patient’s comorbidities, the type of surgery, and conditions that affect the patient’s fluid balance. There is no evidence that colloid is better than crystalloid in the postoperative period, and it is considerably more expensive.\textsuperscript{86} Sepsis and bowel obstruction will require ongoing volume replacement rather than maintenance. Ringer’s solution provides 6 times the intravascular volume as an equivalent amount of hypotonic solution. In patients with normal renal function, clinical signs such as urine output, heart rate, and blood pressure should guide fluid management. Once the stress response subsides, fluid retention subsides and fluid is mobilized from the periphery, and fluid supplementation is unnecessary. This fluid mobilization is evident by decreased peripheral edema and increased urine output. Diuretics given in the period of fluid sequestration may cause intravascular volume depletion and symptomatic hypovolemia.

Postoperative management includes close monitoring of urine output and electrolytes, daily weight, elimination of nephrotoxic medications, and adjustment of all medications that are cleared by the kidney. Hyperkalemia, hyperphosphatemia, and metabolic acidosis may be seen and should be addressed accordingly. Indications for renal replacement therapy include severe intravascular overload, symptomatic hyperkalemia, metabolic acidosis, and complicated uremia (pericarditis and encephalopathy) (Table 2-5).

\textbf{TABLE 2-5: OLIGURIA IN THE PERIOPERATIVE PATIENT}
Postoperative renal failure increases perioperative mortality. Risk factors for postoperative renal failure include intraoperative hypotension, advanced age, CHF, aortic cross-clamping, administration of nephrotoxic drugs or radiocontrast, and preoperative elevation in renal insufficiency. Up to 10% of patients may experience acute renal failure after aortic cross-clamping. Postoperative renal failure rates are higher in hypovolemic patients, so preoperative dehydration should be avoided. Contrast nephropathy is a common cause of hospital-acquired renal failure and manifests as a 25% increase in serum creatinine within 48 hours of contrast administration.

Nephropathy is caused by ischemia and direct toxicity to the renal tubules. Diabetes and chronic renal insufficiency are the greatest risk factors for dye nephropathy. Early trials indicated that patients receiving contrast have a lower incidence of contrast-induced nephropathy when treated with a sodium bicarbonate infusion or N-acetylcysteine. However, recent evidence from multicenter trials and meta-analyses shows no benefit in any pharmacologic intervention in reducing the incidence of radiocontrast nephropathy.

Rising blood urea nitrogen and creatinine and postoperative oliguria (<500 mL/d) herald the onset of postoperative renal failure. Management is determined by the cause of renal insufficiency. Acute renal failure is classified into 3 categories: prerenal, intrarenal, and postrenal. Prerenal azotemia is common in the postoperative period. It is caused by decreased renal perfusion seen with hypotension and intravascular volume contraction. Intrarenal causes of oliguric renal failure include acute tubular necrosis (from aortic cross-clamping, shock, or renal ischemia), and less commonly, acute interstitial nephritis from nephrotoxic medication. Postrenal causes include

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>Intrarenal</th>
<th>Postrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
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<td>Obstruction</td>
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<td>Sepsis</td>
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<td>Dehydration</td>
<td>Myoglobinuria</td>
<td></td>
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<td>Variable</td>
</tr>
<tr>
<td>U_Na</td>
<td>&lt;20 mOsm/L</td>
<td>&gt;50 mOsm/L</td>
<td>&gt;50 mOsm/L</td>
</tr>
<tr>
<td>Fe_Na</td>
<td>&lt;1%</td>
<td>&gt;3%</td>
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</table>

Abbreviations: Fe_Na, fractional excretion of sodium; U_Na, urinary sodium concentration; UOsm, urinary osmolality.
obstruction in the collecting system (from bilateral ureteral injury, Foley catheter occlusion, or urethral obstruction). Workup should include urinalysis, serum chemistries, and measurement of the fractional excretion of sodium. Rarely, invasive monitoring and cardiac echocardiogram may be employed to evaluate volume status. Renal and bladder ultrasound is indicated if obstruction is suspected.

Initial management of oliguria in adults includes placement of a bladder catheter and a challenge with isotonic fluids (500 mL of normal saline or Ringer’s lactate). If a bladder catheter is already present, it should be checked to ensure that it is draining properly. A urinalysis should be obtained with special attention to specific gravity, casts, and evidence of infection. Hematocrit should be evaluated to exclude bleeding and blood pressure measured to rule out hypotension as causes. The fractional excretion of sodium can help determine the etiology of the renal failure (Table 2-5). Serum creatinine is used to follow the course of acute renal failure. Patients who have been adequately resuscitated or who are in CHF require evaluation to rule out cardiogenic shock. Urinary retention can be treated with a Foley catheter, and ureteral obstruction can be addressed with percutaneous nephrostomy.

Intravascular volume depletion adversely affects cardiac output, tissue perfusion, and oxygen delivery. Monitoring includes total body weight, urine output, vital signs, and mental status. However, body weight should not be used alone because total volume overload can be seen in the setting of intravascular volume depletion. Most cases of postoperative renal failure are associated with an episode of hemodynamic instability, and perioperative hemodynamic optimization has been shown to decrease acute kidney injury and mortality. Invasive monitoring to measure cardiac filling pressures may be utilized when clinical assessment is unreliable.

Fluid overload may be seen in patients with renal, hepatic, and cardiac disease and is associated with increased morbidity. Critically ill patients may develop anasarca. It is difficult to determine volume status by observation alone, and invasive monitoring may be required.

Electrolyte abnormalities are common in the perioperative period. Serum sodium reflects intravascular volume status. Hyponatremia signifies excess free water in the intravascular space and is caused by excess antidiuretic hormone in the postoperative period. It occurs in the setting of normo-, hypo-
, or hypervolemia. It may be avoided by judicious use of isotonic fluids. Conversely, hypernatremia suggests a relative deficit of intravascular free water. Patients who are unable to drink or those with large insensible losses are most at risk. Treatment includes free water replacement.

Diuretics, malnutrition, and gastrointestinal losses may cause postoperative hypokalemia. Metabolic alkalosis shifts potassium into the intracellular compartment. Serum potassium levels less than 3 mEq/L warrant ECG monitoring and replacement in patients who are not anuric. Replacement in patients with renal insufficiency may be complex. Hyperkalemia is more commonly seen in renal patients. It may also be seen in myonecrosis, hemolysis, and acidosis. Cardiac arrhythmias are seen at levels above 6.5 mEq/L, and death is associated with levels greater than 8 mEq/L. These patients should have cardiac monitoring until their levels normalize. ECG will show widened QRS interval, peaked T waves, and absent P waves. Hyperkalemia should be treated with sodium bicarbonate to stimulate acidosis, as well as intravenous calcium and insulin with glucose to drive potassium into the intracellular compartment. Cation exchange resins can be administered orally or per rectum to bind ions in the gastrointestinal tract, but care should be taken for the patient who is post–gastrointestinal surgery or has underlying gastrointestinal problems. Dialysis can be employed if other measures fail.

**GLYCEMIC CONTROL**

Hyperglycemia is a risk factor for postoperative infection and perioperative mortality. Intensive insulin therapy (IIT) has been associated with improved outcomes for intensive care unit (ICU) patients, and after cardiac surgery, in brain injury, and after acute MI. However, early enthusiasm for IIT has waned as more recent studies have shown that it is not as beneficial in medical patients as it is in surgical patients and has been associated with severe hypoglycemia. More recently, a meta-analysis of 29 randomized trials of IIT in adult ICU patients showed no difference in mortality in patients receiving IIT versus conventional insulin therapy with goal blood sugar <200 mg/dL. Although there does appear to be consensus that controlling glucose is a worthwhile therapeutic goal in surgical patients in particular, appropriate targets for control remain controversial. While
hyperglycemia is associated with increased infection and mortality. IIT is associated with hypoglycemia and increased mortality. Results from an international, randomized controlled trial in ICU patients demonstrated a 2.6% increase in absolute risk of death in ICU patients with a blood glucose target of 81 to 108 mg/dL versus 180 mg/dL. Others suggest that the variability in glucose level may affect morbidity and mortality more than blood glucose levels alone. More investigation is needed to determine the optimal way to manage blood glucose levels in the postoperative patient.

Our current recommendation for glucose control in noncardiac surgery patients is to maintain blood glucose less than 180 mg/dL.

HEMATOLOGIC EVALUATION

A complete preoperative evaluation should include assessment of hematologic disorders, which can increase the risk for postoperative bleeding or thromboembolism. Patients should be asked about a family history of bleeding disorders and personal history of bleeding problems, especially after procedures. Excessive bleeding after dental procedures and menorrhagia in women can alert the physician to undiagnosed hematologic disease. Risk factors for postoperative hemorrhage include known coagulopathy, trauma, hemorrhage, or potential factor deficiency. Factor deficiencies can be seen with a history of liver disease, malabsorption, malnutrition, or chronic antibiotic use. Even high-risk patients have only a 1.7% risk of postoperative hemorrhage and a 0.21% risk of death related to postoperative hemorrhage.

Routine tests may include a complete blood count, prothrombin time (PT), activated partial thromboplastin time (PTT), and INR, but are not required in the asymptomatic patient with no associated history. The complete blood count will reveal leukocytosis, anemia, and thrombocytopenia or thrombocytosis. A baseline hematocrit is useful for postoperative management when anemia is suspected. Platelet count also provides a useful baseline but does not provide information about platelet function. A bleeding time may be required to provide more information in select patients. However, bleeding time results are operator-dependent and highly variable, making it a poor screening tool for identifying high-risk patients. An abnormal bleeding time is not associated with increased postoperative
nor has it proven useful in identifying patients taking NSAIDs or aspirin. None of the aforementioned tests can be used to diagnose hereditary bleeding disorders. However, an elevated PTT may be seen in factor XI deficiency and should be obtained in patients at risk for this deficiency. Low-risk patients are very unlikely to have bleeding complications even if the PTT is abnormal and have an increased risk of false-positive results that can lead to unnecessary testing. PTT is not a reliable predictor of postoperative bleeding and should not be used to screen for bleeding abnormalities in patients without symptoms or risk factors.

A platelet count of 20,000 or greater is usually adequate for normal clotting. Aspirin causes irreversible impairment of platelet aggregation and is commonly prescribed in patients at risk of cardiovascular and cerebrovascular disease. The clinical effect of aspirin lasts 10 days, and it is for this reason that patients are asked to stop taking aspirin 1 week before elective surgery. Desmopressin can be used to partially reverse platelet dysfunction caused by aspirin and uremia. Other NSAIDs cause reversible platelet dysfunction and should also be held before surgery. Glycoprotein IIb/IIIa inhibitors prevent platelet-fibrin binding and platelet aggregation and are used for 2 to 4 weeks after coronary angioplasty. Elective surgery should be avoided during these 2 to 4 weeks, as stopping treatment increases the risk of thrombosis. Patients who do not receive 4 weeks of antiplatelet therapy are at risk of stent thrombosis.

Indications for red blood cell transfusion remain somewhat controversial and are often empirical in practice. Transfusing 1 unit of red blood cells or whole blood can increase the hematocrit by approximately 3% or hemoglobin by 1 g/dL. Multiple studies have demonstrated that overusing transfusion may adversely affect patient outcome and increase risk of infection. ASA guidelines suggest that transfusion should be based on risks of inadequate oxygenation, rather than a threshold hemoglobin level. Generally, transfusion is rarely indicated when the hemoglobin level exceeds 10 g/dL but is almost always indicated when it is less than 6 g/dL, especially in the setting of acute anemia. Healthy individuals can usually tolerate up to 40% of blood loss without requiring blood cell transfusion, and blood products should not be used solely to expand volume or to improve wound healing. The decision to transfuse red cells or whole blood should be based on the patient’s risk of
complications associated with impaired oxygen delivery, including hemodynamic indices, history of cardiopulmonary disease, rate of blood loss, and preexisting anemia.

Conditions associated with abnormal platelets and low platelet counts can be treated with platelet transfusions. The usual dose, 1 unit of platelet concentrate/10 kg body weight, can be expected to increase the platelet count by approximately 5000 to 10,000 in an average adult. In patients without increased risk of bleeding, prophylactic platelet administration is not indicated until counts fall below 20,000. Higher thresholds may be indicated for patients at increased risk of bleeding or with known platelet dysfunction or microvascular bleeding. Desmopressin can augment platelet function in uremia and incite release of von Willebrand factor (vWF) from the endothelium, which can improve platelet function. The decision to transfuse platelets should be based on the amount of bleeding expected, the ability to control bleeding, and the presence of platelet dysfunction or destruction.

Transfusion of fresh frozen plasma (FFP) is indicated to reverse warfarin before procedures or in the presence of active bleeding, for inherited or acquired coagulopathy that can be treated with FFP, and for massive transfusion of more than 1 whole blood volume. Microvascular bleeding can be seen if the PT/PTT is greater than 1.5 times normal, and FFP can be used to reverse bleeding in this setting. Warfarin reversal can be achieved with doses of 5 to 8 mL/kg, and 30% factor concentration can be achieved with 10 to 15 mL/kg. FFP should not be used to address volume depletion alone. Cryoprecipitate contains factors VIII, vWF, XIII, fibrinogen, and fibronectin, and can be used preventively in patients with these factor deficiencies and uremia.

Endothelial injury and venous stasis are the greatest risk factors for VTE. The patient with hereditary thrombophilia or a personal history of VTE, cancer, or recent surgery (within 4 weeks) has an increased risk of VTE. Preventive measures include external pneumatic leg compression, early mobilization after surgery, and anticoagulation. Compression devices are contraindicated in patients with severe peripheral vascular disease, venous stasis, or risk of tissue necrosis. Inferior vena cava (IVC) filters are indicated in patients who cannot take anticoagulation or who have failed anticoagulation therapy. Patients with a history of VTE benefit from IVC filter placement in the short term, but IVC filter placement is accompanied by an increased incidence of deep venous thrombosis over the long term.
Systemic anticoagulation is the preferred long-term option. LMWH and UFH are equally effective for prevention of pulmonary embolism in patients with deep venous thrombosis.\textsuperscript{107} Recent VTE, atrial fibrillation, and mechanical heart valves are common indications for warfarin treatment.

Clinically, UFH activity is measured by PTT, and the therapeutic goal is usually 2.0 to 2.5 times normal. LMWH is a relatively stronger inhibitor of factor Xa and does not have the same effect on the PTT. The anticoagulant effect of LMWH is measured by factor Xa activity. Protamine can reverse the effects of heparin but may cause allergic reactions and induce hypercoagulability and should be used cautiously. FFP will not reverse heparin and can actually increase heparin activity because it contains antithrombin III. Direct thrombin inhibitors can also prolong the PTT. Direct thrombin inhibitors are not reversible with protamine and may require large amounts of FFP for reversal.

Heparin can be used for the prevention and treatment of VTE. Surgical patients over age 40 or those at increased risk for VTE should receive 5000 U subcutaneously every 8 to 12 hours, depending on their weight. High-risk patients with a history of VTE, cancer, or morbid obesity or those having orthopedic procedures should either receive subcutaneous heparin with a goal of high range of normal or LMWH. In the event of acute VTE, intravenous heparin should be started promptly with a therapeutic PTT goal of 1.5 to 2.0 times normal. Oral anticoagulation should be started within 24 hours and continued for 3 to 6 months.\textsuperscript{106}

Heparin-induced thrombocytopenia (HIT) is a potentially lethal complication of heparin therapy. HIT is caused by an immunoglobulin G–mediated hypersensitivity reaction between the heparin moiety and platelet factor 4 (PF4). Patients with previous heparin exposure, such as orthopedic and cardiac surgical patients, are at greatest risk. The incidence of HIT is 0.5% to 5.0% in patients receiving UFH. HIT occurs with UFH or LMWH; the risk is highest with UFH.

Platelet counts usually drop 40% to 50% from baseline. Thrombosis can be venous or arterial, leading to deep vein thrombosis, extremity ischemia, and mesenteric ischemia of stroke. Digital ischemia and skin necrosis can also be seen. HIT remains a clinical syndrome that can be diagnosed by a decrease in platelet count <40% of baseline in 4 to 14 days of heparin administration once other causes of thrombocytopenia have been ruled out. The diagnosis can be supported by the enzyme-linked immunosorbent assay

\textsuperscript{107}
for antiplatelet antibodies.

Because HIT can be life-threatening, heparin should be stopped as soon as HIT is suspected, and treatment with an alternative anticoagulant, such as the thrombin inhibitor bivalirudin, should be started immediately. Platelets should return to baseline after therapy is initiated. If thrombosis is present, patients should be anticoagulated for 6 months with warfarin. Warfarin should not be started until platelet counts have recovered.

Warfarin inhibits synthesis of vitamin K–dependent clotting factors (II, VII, IX, X, and proteins C and S). Poor diet, prolonged antibiotic use, and fat malabsorption can also cause vitamin K deficiency and cause abnormal coagulation. Liver disease can lead to multiple coagulation abnormalities including factor deficiencies, vitamin K deficiency, fibrinolysis, and elevated levels of fibrin degradation products. All patients with known or suspected liver disease should be tested for coagulopathy. Vitamin K can be administered subcutaneously or intravenously in deficient patients. The initiation of warfarin therapy is associated with a transient thrombotic state because plasma concentrations of protein C fall approximately 24 hours before concentrations of other clotting factors.

Heparin is the drug of choice for VTE during pregnancy because it does not cross the placenta. Adverse effects of heparin therapy may include hemorrhage, thrombocytopenia, and osteoporosis. HIT is an immune disorder seen in patients with prior exposure to heparin, which may cause thrombosis. Treatment includes cessation of heparin and utilization of alternative anticoagulants such as lepirudin, danaparoid, or argatroban. These should be given until platelet counts recover.

For patients on long-term anticoagulation therapy, the INR should be 1.5 or lower before elective surgery. After warfarin is discontinued, it takes about 4 days for an INR in the range of 2.0 to 3.0 to spontaneously reach 1.5, and about 3 days for the INR to reach 2.0 after it is restarted. If therapy is withheld preoperatively, most patients will have a window of 2 to 4 days when they are not anticoagulated and at risk for venous thrombosis. This risk is compounded by the increased risk of thromboembolism associated with surgery.\textsuperscript{108,109} It has been estimated that surgery increases the risk of VTE by 100-fold in patients with recurrent disease.\textsuperscript{110} Without anticoagulation, there is a 50% chance of recurrence within the 3 months after the first episode of venous thrombosis. Warfarin therapy reduces the risk to 10% after 1 month and 5% after 3 months. It is not advisable to interrupt anticoagulation within
1 month after an event of VTE, and if possible, surgery should be deferred until the patient has completed 3 months of therapy. Chronic anticoagulation lowers the risk of thromboembolism in patients with atrial fibrillation and mechanical heart valves by 66% and 75%, respectively.

Patients with prior embolic episodes are at increased risk for recurrence. Six percent of episodes of VTE and 20% of arterial thromboembolisms may be fatal, and a significant percentage cause disability. Alternatively, the risk of death after postoperative hemorrhage is less than 1%, so the judicious use of postoperative anticoagulation can be relatively protective. Preoperative heparinization is not required during the second and third months of warfarin treatment for deep vein thrombosis because the risk is sufficiently low. Such patients have increased VTE risk after surgery and should receive postoperative anticoagulation. Patients who are at risk for recurrent deep vein thrombosis and are within 2 weeks of the first episode or who cannot tolerate anticoagulation are candidates for an IVC filter.

Elective surgery should be deferred for the first month after arterial embolism because of the high risk of recurrence during this period. If necessary, patients should receive perioperative heparin while oral anticoagulation is held. Patients on long-term anticoagulation to prevent arterial thromboembolism do not need perioperative heparin because the risk of bleeding outweighs the risk of arterial embolism during this period.

Heparin should be titrated to a goal PTT of 1.5 to 2.0 times normal and given as a continuous intravenous infusion. It should be stopped 6 hours prior to a procedure and can be restarted 12 hours after surgery if there was no evidence of bleeding at the end of the case. Heparin can be restarted without a bolus at the anticipated maintenance infusion rate.

INFECTIONOUS COMPLICATIONS

Infectious complications can be most unwelcome and difficult to control after major abdominal surgery, yet they are surprisingly frequent despite all modern prophylactic measures. Reported surgical wound infection rates in elective operations vary from 2% for inguinal hernia repair, to 26% for colectomy, and is even higher for emergency surgery. Surgical site infections (SSIs) increase overall mortality and morbidity and increase hospital length of stay and overall costs. Therefore, prevention and treatment...
of infectious complications should be included in surgical decision-making for all abdominal procedures.

Prevention of SSIs begins with preoperative evaluation and identification of patients at high risk for SSI. Patient factors implicated in risk of SSI include age, diabetes mellitus, smoking, steroid use, malnutrition, obesity, active distant infection, prolonged hospital stay, and nasal colonization with *Staphylococcus aureus*.115-118

Standard basic surgical rules should be followed with every patient. These were codified as formal guidelines by the Centers for Disease Control and Prevention (CDC) and updated in 2017119 and include recommendations for skin preparation with alcohol-based skin antiseptics, surgical barriers such as drapes and gowns, careful hand scrubbing, and appropriate selection of prophylactic antibiotics. Preoperative hair removal and antiseptic shower have not been shown to decrease SSI rates, and shaving and clipping of hair can increase SSIs. The CDC recommendations are summarized in Table 2-6.

<table>
<thead>
<tr>
<th>TABLE 2-6: CDC CATEGORY 1 RECOMMENDATIONS FOR REDUCTION OF SURGICAL SITE INFECTIONS</th>
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<tr>
<td><strong>These are strongly recommended based on best clinical evidence:</strong></td>
</tr>
<tr>
<td>Identify and treat distant infections prior to surgery</td>
</tr>
<tr>
<td>Do not remove hair routinely; if hair must be removed, use electric clippers immediately prior to surgery</td>
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<tr>
<td>Control hyperglycemia in the perioperative period</td>
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<tr>
<td>Cease tobacco smoking 30 days prior to surgery</td>
</tr>
<tr>
<td>Antiseptic shower the night prior to surgery</td>
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<tr>
<td>Antiseptic skin preparation</td>
</tr>
<tr>
<td>Surgery team should practice hand scrubs</td>
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<tr>
<td>Administer appropriate antimicrobial prophylaxis</td>
</tr>
<tr>
<td>Surgical barriers (gown, gloves, hat, mask)</td>
</tr>
<tr>
<td>Do not close contaminated skin incisions</td>
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</table>

Antibiotic prophylaxis may be indicated for patients at high risk or in contaminated surgical procedures, but antibiotics should not be used indiscriminately. Overuse of antibiotics is associated with emergence of
multidrug-resistant bacteria and increased rates of hospital-acquired infections. Selection of patients for antimicrobial prophylaxis requires stratification of patient risk factors, as discussed above, and procedure-specific risk factors. The degree of contamination in the surgical site has long been recognized as an independent risk factor for SSI, leading to the wound classification system (Table 2-7) in use since 1983.

**TABLE 2-7: SURGICAL WOUND CLASSIFICATION**

**Class I. Clean**
Uninfected wounds without contamination

**Class II. Clean/Contaminated**
Uninfected wounds in procedures where the respiratory, gastrointestinal, or genitourinary tracts are entered in a controlled fashion without gross spillage

**Class III. Contaminated**
An operation with major breaks in sterile technique, gross spillage, or incisions into inflamed but not suppurating infections; fresh accidental wounds

**Class IV. Dirty/Infected**
Wounds with necrotic or devitalized infected tissue

Patients undergoing class I (clean) procedures have a very low infection rate and generally do not benefit from prophylactic antibiotics, unless there is some suspicion at the start of the procedure that some contamination may occur, such as unplanned enterotomy in a patient with many previous abdominal procedures. In addition, many surgeons prefer to use antibiotic prophylaxis in class I procedures when a prosthesis is implanted; examples include hernia repair and vascular bypass. In this setting, the risk of SSI is low, but the morbidity and mortality of an infected prosthesis are great, and prophylaxis may decrease the risk. To date, large prospective trials have not shown benefit of antibiotic prophylaxis in preventing prosthetic infections, but smaller trials have suggested a decrease in site infection without change in implant infection rate. Therefore, there is no strict
guideline for the use of systemic antibiotics for implant surgery, and the surgeon must tailor the use of antibiotics to the individual patient’s risk.

Patients with class II (clean/contaminated) surgical wounds do benefit from systemic antibiotic prophylaxis. The most studied example of this class of wound is elective colon resection. Most current guidelines recommend systemic broad-spectrum antibiotic coverage using a second-generation cephalosporin plus metronidazole, if the parenteral route is used, and neomycin plus metronidazole or erythromycin base (both as nonabsorbable antibiotics), if the oral route is used.\textsuperscript{125} Published evidence supports administration of antibiotics preoperatively in order to achieve maximum therapeutic levels at the time of incision and continuation of the antibiotic dosing schedule to maintain therapeutic levels during a long procedure. There is no documented study showing benefit to additional doses of antibiotics after the procedure is over and the skin is closed, and prolonged use of prophylactic antibiotics contributes to emergence of resistant bacteria.\textsuperscript{126,127}

Patients with class III (contaminated) wounds are a mixed population. Some of these wounds are the result of inadvertent entry into a contaminated field, some result from traumatic injury, and some are planned operations for débridement of infected tissue. In the latter case, antibiotic therapy is indicated for specific therapy rather than prophylaxis. In the case of penetrating traumatic injury to the colon, there is strong evidence to support single-dose antibiotic prophylaxis at the time of laparotomy, similar to elective colon resection.\textsuperscript{128,129} Surgical judgment must be individualized in these cases as to whether the risk of skin closure can be justified due to the high rate of wound infection despite antibiotic prophylaxis.

Patients with class IV (dirty) wounds are generally undergoing débridement of already infected and necrotic tissue and should be receiving antibiotic therapy targeted to the relevant organisms. Skin wound closure is generally not advised in these patients.

The wound classification system does not take into account patient risk factors or site-specific risk factors. Various physiologic scoring systems including the Acute Physiology Score and the Acute Physiology, Age, and Chronic Health Evaluation index have been used to predict perioperative infection risk with some success. In an effort to provide more accurate risk stratification, the CDC’s National Nosocomial Infection Surveillance project has developed a risk index that accounts for patient risk factors, such as
malnutrition and chronic medical conditions, and operative factors, including duration and site of procedure. Enlightened risk assessment of perioperative infections should be included in the discussion for informed surgical consent.

**NUTRITIONAL EVALUATION**

The importance of proper nutritional assessment and management cannot be overstressed. In surgical patients, malnutrition increases risk for major morbidity, including wound infection, sepsis, pneumonia, delayed wound healing, and anastomotic complications. Careful preoperative clinical assessment can identify patients at increased nutritional risk. The assessment should include a thorough history and physical exam with attention paid to usual weight, recent weight loss, changes in eating and bowel habits, changes in abdominal girth, loss of muscle bulk, and the presence of diseases that carry a risk of malnutrition such as COPD, diabetes mellitus, inflammatory bowel disease, and psychiatric conditions such as bulimia and anorexia nervosa. The history and physical exam should identify patients with nutritional risk; that risk can be stratified by calculation of the Nutritional Risk Index (NRI). The NRI is a simple calculation (15.19 × serum albumin [g/dL] + 41.7 × present weight/usual weight) that has been shown in prospective studies to correlate with increased rates of mortality and complications from major abdominal surgery. NRI less than 83 indicates a significantly increased rate of mortality and complications, especially wound dehiscence and infection. Severely malnourished patients have been shown to benefit from preoperative nutritional support.

Malnutrition can be classified into protein deficiency (kwashiorkor), calorie deficiency (marasmus), or mixed protein-calorie deficiency. To complete the nutritional assessment and to guide nutritional support, it is useful to classify the patient’s specific nutritional state (Table 2-8). Malnutrition states are much more common than is generally acknowledged, with 30% to 55% of hospital inpatients meeting criteria for one of these diagnoses.

**TABLE 2-8: ASSESSMENT OF NUTRITIONAL STATUS**
Protein Deficiency Criteria
Albumin <2.2 g/dL
Total lymphocyte count 800/µL or less
Weight maintained
Peripheral edema
Inadequate protein intake (<50% of goal for 3 days or <75% for 7 days)
Four criteria out of these five establish the diagnosis of protein deficiency

Calorie Deficiency Criteria
Weight loss: 5% over 1 month or 7.5% over 3 months or 10% over 6 months
Underweight: <94% ideal body weight
Clinically measurable muscle wasting
Serum protein maintained
Inadequate calorie intake (50% for 3 days or <75% for 7 days)
Three criteria out of these five establish diagnosis of caloric deficiency

Mixed Protein-Calorie Malnutrition Criteria

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<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Weight loss</td>
<td>5%-9%</td>
<td>10%-15%</td>
<td>10%-15% over 6 months</td>
</tr>
<tr>
<td>Underweight</td>
<td>94%-85%</td>
<td>84%-70%</td>
<td>&lt;70% ideal weight</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.8-3.4 g/dL</td>
<td>2.1-2.7 g/dL</td>
<td>&lt;2.1 g/dL</td>
</tr>
<tr>
<td>Total lymphocytes</td>
<td>1499-1200/µL</td>
<td>1199-800/µL</td>
<td>&lt;800/µL</td>
</tr>
<tr>
<td>Transferrin</td>
<td>199-150 mg/dL</td>
<td>149-100 mg/dL</td>
<td>&lt;100 mg/dL</td>
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To establish the diagnosis of mild or moderate protein-calorie malnutrition, 2 of the 5 criteria shown must be met; to establish the diagnosis of severe protein-calorie malnutrition, 3 of the 7 criteria must be met.

Some interval of deficient nutritional intake is expected after an abdominal operation. In uncomplicated cases, this is usually the result of postoperative adynamic ileus and resolves promptly, in less than 7 days. Traditional surgical management includes provision of dextrose-containing intravenous fluids. The goal of this therapy is not to provide sufficient calories for complete nutritional support, but simply to provide enough carbohydrate to prevent breakdown of lean body mass. Certain organs, including the heart and brain, have an obligate requirement for carbohydrate as a primary energy source and do not store energy in the form of fat or glycogen. If intake is insufficient to meet this requirement, the body breaks down hepatic glycogen to provide glucose to the circulation, and ultimately the brain and heart. Once hepatic glycogen stores have been depleted (after about 1 day of no intake), lean muscle mass is converted to glucose via gluconeogenesis to produce carbohydrate. Provision of only 100 g of exogenous glucose per day is sufficient to prevent breakdown of lean muscle mass in otherwise healthy subjects.

In already malnourished patients or in patients who do not return to normal bowel function promptly, nutritional support is indicated. As in the preoperative setting, a thorough evaluation of the patient’s nutritional status is necessary, as is the identification of the cause of bowel dysfunction. In the
postoperative setting, there are many potential causes of bowel dysfunction (Table 2-9), and nutritional support should be individualized for each patient’s needs. Some patients may respond to enteral support, and some may require parenteral support. Whenever available, the enteral route is the preferred route of support, as it has been shown to cause less morbidity and mortality.138

<table>
<thead>
<tr>
<th>TABLE 2-9: POSTOPERATIVE CAUSES OF DEFICIENT NUTRITIONAL INTAKE</th>
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<tr>
<td>Ileus</td>
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<tr>
<td>Bowel obstruction</td>
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<td>Colitis (ischemic, infectious)</td>
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<tr>
<td>Fistula</td>
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<tr>
<td>Dysphagia</td>
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<tr>
<td>Gastric dysmotility</td>
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<td>Intestinal insufficiency (short-gut syndrome)</td>
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Enteral nutritional support is effective in patients who have functional small bowel; examples include esophageal or gastric resection, patients with postoperative delirium or dysphagia, and patients who have gastroparesis. In the short term, if the dysfunction is expected to respond to treatment, nasogastric tubes can be used effectively to deliver full support. Patients who need long-term enteral support are best served with gastrostomy or jejunostomy tubes, which may be placed operatively or percutaneously. With good preoperative nutritional assessment and sound surgical judgment, these patients’ needs for long-term postoperative support can often be anticipated, and long-term feeding access can be included in the operative plan. Enteral support may not be suitable for some patients; examples include early postoperative bowel obstruction, fistula, or intestinal insufficiency (short-gut syndrome). In such patients, parenteral support is indicated and should be initiated without delay, and futile attempts to use the enteral route should be avoided.

Irrespective of the route of support, every patient on nutritional support should have his or her nutritional needs assessed and provided. The
assessment begins with the calorie requirement. There are several formulas and nomograms that estimate basal energy expenditure, accounting for height, weight, age, sex, stress factors, and activity factors. All of these methods are estimations and may underfeed or overfeed certain subgroups, especially the obese. The method in most common clinical use bases basal energy expenditure on adjusted body weight (ABW). Using this method, ABW is defined as the patient’s ideal body weight plus the difference between actual body weight (BW) and the ideal body weight (IBW) divided by 2:

\[
ABW = IBW + 0.5(BW – IBW)
\]

The baseline caloric requirement for weight maintenance based on ABW is 25 kcal/kg/d. This target may be adjusted upward in patients with extreme metabolic demands, as is the case in burns or head injury. Furthermore, the ABW can be used to establish the protein requirement. In unstressed normal subjects, the minimum daily protein requirement is 0.8 g protein/kg/d. In postoperative patients with healing wounds, this target is adjusted to 1.0-1.5 g/kg/d, and in severely ill patients to 2.0 g/kg/d. The highest requirements are seen in severe burn and bone marrow transplant patients.

Essential nutritional components must be provided, again irrespective of the route of support. These include water- and lipid-soluble vitamins, trace elements such as zinc and selenium, essential fatty acids such as linoleic and linolenic acids, and the 8 essential amino acids. These trace elements are provided in abundance in all enteral feeds and are part of the standard additives in parenteral formula.

Once nutritional support has been initiated, the patient’s response to support must be followed closely, especially in parenteral support and in patients with preexisting metabolic conditions such as diabetes. Blood glucose should be monitored regularly during the first few days of support. Recent evidence has linked hyperglycemia in the postoperative setting, especially in critically ill patients, with increased risk of death and infection. In addition, electrolyte abnormalities (especially those of potassium, magnesium, and phosphate) are often seen in the early period of nutritional support and should be corrected.

It is also important to follow the markers of nutrition repletion to ensure that the calories and protein provided (based on the initial estimate) are
sufficient and the patient is not mobilizing lean body mass due to inadequate support. Serum markers such as prealbumin, retinol-binding protein, and transferrin can be useful in this regard. They are serum proteins with short (2-7 days) turnover times that reflect the body’s ability to synthesize new protein. Unfortunately, the serum concentrations of these proteins are also affected by acute disease states and renal and hepatic failure and can be difficult to interpret in postoperative patients. Nitrogen balance can also be used to monitor nutritional support and reflects the ability to synthesize new protein. Nitrogen balance is calculated by subtracting nitrogen excretion from nitrogen intake. Nitrogen intake is calculated from the protein intake, where each gram of protein/6.25 = the number of grams of nitrogen. Nitrogen excretion has 2 components: urinary urea nitrogen (UUN) and insensible loss. UUN can be measured in a 24-hour urine collection; insensible loss is generally accepted to be 4 g/d, unless there is another source of loss, such as abdominal drainage of proteinaceous ascites, enterocutaneous fistula, or nephrotic syndrome. Thus, in most cases, nitrogen balance can be simplified to:

\[
\text{Nitrogen balance} = \frac{\text{protein intake}}{6.25} - \text{24-hour UUN} - 4 \text{ g (insensible loss)}
\]

A patient who takes in more nitrogen than he or she excretes in the urine and feces is in positive nitrogen balance and is synthesizing new protein. On the other hand, a patient who is excreting more nitrogen than he or she is receiving in nutritional support is in negative nitrogen balance and is therefore losing lean body mass, becoming more malnourished. These patients should be reevaluated for nutritional needs and for sources of nutritional depletion, such as uncontrolled diabetes mellitus, sepsis, and organ failure.

By itself, uncontrolled diabetes mellitus can be viewed as a perioperative nutritional complication, as it results in nutritional depletion, interferes with delivery of parenteral and enteral nutrition, and is associated with increased infectious morbidity.

**COMPREHENSIVE PERIOPERATIVE MANAGEMENT PATHWAYS**
Enhanced recovery after surgery (ERAS) pathways have been proposed for the purpose of cost containment, standardization of care, and improvement of surgical outcomes. Initially advanced for elective procedures, especially partial colectomy, these pathways are increasingly being applied to diverse procedures in the elective and emergent setting. The pathways are not universally standardized, but several international societies have published guidelines for the composition of ERAS pathways for elective colon resection based on best evidence-based practices.

For elective colon resection, the ERAS Society has developed a comprehensive, evidence-based bundle of guidelines that include specific recommendations for smoking cessation, preoperative carbohydrate loading (for nondiabetics), intravenous antibiotic prophylaxis, postoperative nausea and vomiting management, core body temperature management, fluid restriction, VTE prophylaxis, and others. Adoption of an ERAS pathway has been associated with shortened length of hospital stay and improved outcomes in colorectal surgery in randomized prospective trials, which has led to implementation of the ERAS approach in other procedures.

It should be noted that the concept of the pathway is that each pathway is specific to a given procedure and no universal ERAS pathway has been investigated.

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28. Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary


INTRODUCTION

Enhanced recovery protocols (ERPs) were developed primarily for the care of the colorectal surgical patient during the late 1990s and demonstrated early success in the 2000s.\textsuperscript{1-7} These efforts represented consensus from dieticians, nurses, surgeons, and anesthesiologists at the time and ultimately grew into codified components of care with excellent outcomes.\textsuperscript{8-11} This work truly represents the culmination of the best science that has assessed the surgical stress response and mitigating therapies, principally from the work of Henrik Kehlet who deserves the title of “Father of Enhanced Recovery After Surgery.”\textsuperscript{8} ERP implementation has evolved from a convoluted and often complex set of care plans to a true discipline for evidence-based care of the surgical patient. Although the early focus was on length of stay, the science
has evolved into an approach for improved patient-centric care that deserves the more proper title of “enhanced recovery protocols” (ERPs). The concepts related to preoperative cardiovascular and pulmonary risk assessment and risk modification are well defined by surgical and anesthesia textbooks and preoperative anesthesia clinic processes, and although they are clearly an essential part of a strong perioperative care plan, they are not typically considered ERP components of care. The majority of a gastrointestinal (GI) surgery–related ERP consists of a variety of shared components that will be addressed in a later section. These strategies are designed to recognize and optimize preoperative physiologic adverse factors, the perioperative stress response, narcotic-sparing analgesia, evidence-based reduction of “potentially preventable complications,” early and aggressive ambulation, and early return to enteral intake.\(^3\)\(^,\)\(^8\) The optimal use of these strategies has consistently demonstrated a significant reduction in hospital stay and costs, while significantly improving patient safety. The potential components of care include preoperative assessment and education, nutritional repletion, improvement in perioperative glycemic management, anesthesia/analgesia, goal-directed fluid therapy, prevention of nausea and ileus, thromboembolic prophylaxis, minimally invasive techniques, temperature monitoring, early postoperative nutrition, and early mobilization.\(^2\) The net result of a well-developed program with a high degree of institutional compliance has been a universal improvement in clinical outcomes, reduced length of stay, reduced cost, and most importantly, significantly improved physical recovery of the patient.\(^5\)\(^,\)\(^9\) An interesting institutional journey is reflected in the work by Bakker et al,\(^10\) who determined that the strongest predictors for a shorter duration of stay (5.7 days with high compliance vs 7.3 days with low compliance) were no nasogastric tube, early mobilization, early oral nutrition, early removal of epidural, early removal of catheter, and nonopioid oral analgesia. However, despite the institutional recognition of these fairly simple components of care and the benefits, the mean adherence rate was 73% in 2006 and 2007, 66% in 2008 and 2009, 63% in 2010 and 2011, and 82% in 2012 and 2013.\(^10\) This implies that constant monitoring of both process and outcome is essential for durable success with ERPs.

Despite the almost 20-year recognition of the benefits of ERP, the current adoption rate of programs remains disappointingly low.\(^9\) The low adoption rate is a function of a lack of understanding related to the relative impact of
various components of the plan, the perceived complexity of delivering the components, and most significantly, clinicians’ unwillingness to change behavior in the face of incontrovertible evidence. The purpose of this chapter is (1) to define the mutually shared components across GI surgery ERPs and the rationale for these components; (2) to define procedure- and discipline-specific components of care; (3) to review the clinical and financial benefits in favor of ERPs; and (4) to review issues around adoption of ERPs at an institutional level. This chapter will review the shared components of GI surgery–related ERPs and the nuances related to esophageal, gastric, bariatric, liver/biliary, pancreatic, and colorectal surgery.

**SHARED COMPONENTS OF ERPS**

The Enhanced Recovery After Surgery (ERAS) Society ([www.erassociety.org](http://www.erassociety.org)) has published multiple guidelines related to GI surgery, and the reader is referred to 2 major society websites focused on ERP that provide a variety of documents for open access to ERP plans (American Society of Enhanced Recovery at [aserhq.org](http://aserhq.org) and Society of American Gastrointestinal and Endoscopic Surgeons at [www.sages.org/smart-enhanced-recovery-program/](http://www.sages.org/smart-enhanced-recovery-program/)). The organizations provide analyses and quality rankings of the various data elements that can be interpreted by individual healthcare systems for relative benefits for local implementation. It is intriguing that despite the large database available to the ERAS Society, little has been published on actual outcomes, unlike the ubiquitous National Surgical Quality Improvement Program (NSQIP)–related publications. Once again, the attempt to assess the long lists of multiple components on these sites can be intimidating early in the process development of an organization that requires sometimes cumbersome change management strategies. It is well beyond the scope of this chapter to discuss the complex science of change management, but it is clear that a strategy of rapidly assessing current outcomes and implementing an aligned strategy can lead to rapid process improvement. This chapter will attempt to organize components of an ERP strategy into the following components of the episode of care to allow systems to assess the requisite integration of care required: preadmission; day of surgery; and intraoperative, postoperative, and discharge planning.

The major impediments to successful implementation are typically system
based and due to fragmented care delivery and debates over the validity of one or another element. The experience by Nelson et al and his colleagues in Alberta, Canada, which provided regular outcomes data, may be an effective means to overcome resistance. Particularly in the United States, the lack of economic integration and therefore structural integration can increase the difficulties of change management. The lack of economic integration is also challenging because some components of the plan need to be administered before admission and, therefore, are not bundled into hospital payments, resulting in patient out-of-pocket costs that are not typically reimbursed. This is a significant stumbling block to the successful compliance with components such as immunonutrition and carbohydrate loading. Another important obstacle is the perceived need for complex risk adjustment models. In fact, US hospitals can access the important cost drivers of care using the readily available and routinely submitted administrative data. Alternatively, many hospitals participate in national programs, such as NSQIP or the Vizient programs, which provide easily accessible and robust data related to both outcomes and cost. It should be a relatively easy discussion to review high-impact negative outcomes and, in the true spirit of quality improvement, implement a plausible solution and in rapid sequence assess change in outcome. An example of how difficult this approach can be is exemplified by the work of Harbaugh et al assessing the only US Food and Drug Administration–approved prophylactic agent for reduction postoperative ileus (POI), which demonstrated that even across members of an advanced quality collaborative, adoption of a component with proven benefits is highly variable.

**Preadmission**

**ANEMIA**

Preoperative anemia occurs frequently in GI surgical patients as a result of chronic blood loss, nutritional deficiencies (typically iron), and the impact of neoadjuvant oncologic treatment. Conversely, outside of emergency surgery, which has a separate set of strategies for blood conservation and repletion, the preoperative period provides a sufficient time frame to address preexisting anemia. Preoperative anemia and blood transfusions are associated with a higher incidence of postoperative infections, a longer
hospital stay, higher cost, and a worse overall outcome.\textsuperscript{29,30} Iron deficiency anemia is by far the most frequent form of preoperative anemia, is particularly common among the elderly population, and is readily evaluated and treated in a time-compressed manner.\textsuperscript{31,32} The opportunity for a system to include routine complete blood count and reflex to specific iron studies based on specific thresholds can lead to a cost-effective and efficient means of identifying at-risk patient populations.\textsuperscript{33,34} Incorporation of this type of testing strategy can further lead to an integrated approach to effective treatment with iron infusions and a reduction in the need for perioperative transfusions.\textsuperscript{35,36}

**SARCOPENIA**

Sarcopenia is a common adverse risk factor for a variety of GI surgical procedures.\textsuperscript{37-41} Once again, the ability to identify this risk factor is readily available as virtually all GI surgery patients are evaluated with abdominal computed tomography and the nomograms are well accepted. A typical algorithm is the use of a single slice at the level of the third lumbar vertebra (L3) or the measurement of total fat area (cm\(^2\)), subcutaneous fat area (cm\(^2\)), visceral fat area (cm\(^2\)), and skeletal muscle area (cm\(^2\)) using accepted Hounsfield unit (HU) thresholds (adipose tissue, −190 to −30; skeletal muscle, −29 to +150). These parameters are then normalized for patient stature and designated as total fat index (cm\(^2/m^2\)), subcutaneous fat index (cm\(^2/m^2\)), visceral fat index (cm\(^2/m^2\)), and skeletal muscle index (cm\(^2/m^2\)) in line with accepted methodology.\textsuperscript{42,43} Sarcopenia is defined as a skeletal muscle index <43 cm\(^2/m^2\) for males and <41 cm\(^2/m^2\) for females using previously published cutoff values.\textsuperscript{44} Unfortunately, despite the growing recognition of the frequency and significant impact of sarcopenia, there is surprisingly little information in the surgical literature regarding the appropriate method for repletion and/or the ability to reverse some percentage of the physiology in a time-compressed manner to influence surgical outcomes.

Current treatment strategies are designed to address nutritional supplementation of proteins, essential amino acids, and fatty acids, combined with focused resistance training and physical activity. Skeletal muscle possesses an inherent capacity for regeneration due to activation of resident
satellite cells and is regulated in part by host innate immune responses, especially the macrophage response.\(^\text{45}\) In addition, muscle wasting in the surgical patient can also be associated with chronic inflammatory diseases and the related pathophysiologic impact of proinflammatory cytokines including interferon-\(\gamma\), interleukin (IL)-1, tumor necrosis factor-\(\alpha\), IL-6, IL-18, and IL-8.\(^\text{46}\) This information is essential to understand the current gap in the ERP literature regarding the potential benefits of a specific regimen.\(^\text{47,48}\) A number of meta-analyses regarding the assessment of immunonutrition have been published; however, virtually all of the data are from a period of time prior to adoption of ERPs, leading to conflicting outcomes when recent data are included.\(^\text{49-54}\) This gap is highlighted by the meta-analysis performed by Hegazi et al,\(^\text{52}\) which assessed 8 randomized controlled trials (RCTs) of preoperative immunonutrition versus standard enteral therapy and 9 RCTs of immunonutrition versus no supplements.\(^\text{52}\) The authors found no advantage with immunonutrition over standard protein supplementation. Similarly, the comparison of 3 recent studies demonstrates the same conundrum regarding the benefits of supplement components within an ERP. Moya et al\(^\text{55}\) randomized patients to receive either no supplement or immunonutrition and reported a reduction in surgical site infection (SSI) in the absence of a mechanical bowel preparation (MBP) or antibiotic bowel prep. Hübner et al\(^\text{56}\) randomized patients undergoing elective major GI surgery to either immunonutrition or isocaloric isonitrogenous nutrition given for 5 days preoperatively within an ERAS pathway and demonstrated no improvement in outcomes. Finally, Thornblade et al\(^\text{57}\) conducted a retrospective assessment of a quality database that assessed a population that received recommendations for usage of a preoperative supplement but provided no data on degree of compliance and suggested outcomes were better with the recommendation. These data are further complicated by recent data suggesting that glutamine, arginine (vs citrulline), and omega-3 fatty acids are associated with either increased risk or no benefit in many stressed patient populations.\(^\text{58-65}\) The current data suggest that the commonly recommended supplements seeking to address benefits related to immunonutrition likely do not provide the mix of low carbohydrate, high leucine, and vitamin D components that appear optimal for sarcopenia.\(^\text{66-69}\) Therefore, at this time, the data suggest that patients should be investigated for the presence of sarcopenia and that patients with sarcopenia will benefit from a supplement
versus no supplement. It remains unclear what the refinements in supplementation will be over time as well as what the relative benefits of immunonutrition are for nonsarcopenic and normally nourished patients.

CARBOHYDRATE LOADING

At least 15% to 35% of patients undergoing major general, gynecologic, urologic, cardiothoracic, and orthopedic surgery will experience significant hyperglycemia in the immediate preoperative period, even if they are not diabetic. Postoperative hyperglycemia in nondiabetics is associated with at least a 2-fold increase in the risk of both surgical site infection (SSI) and mortality. The risk of postoperative hyperglycemia is exacerbated by the commonly used and unnecessarily prolonged preoperative period of no oral intake (NPO), which creates a starvation-induced insulin resistance and gluconeogenesis response. Most ERPs recognize the risk associated with a prolonged NPO period and recommend the provision of a maltodextrin-containing beverage both the evening before and just 2 hours prior to surgery. The concept of perioperative “carbohydrate loading” is frequently misunderstood, and practitioners may rely on sports drinks designed to support athletic-induced carbohydrate consumption from muscle activation and the associated dehydration. The administration of simple sugars (especially fructose) using fruit juices or sports drinks delivers an excessive glycemic index load, resulting in rapid and early glucose and insulin spikes followed by compensatory glucagon secretion, which does not improve insulin sensitivity. As a result, there are no published data assessing the impact of these products on “perioperative carbohydrate loading.”

Several studies using euglycemic clamp have demonstrated improved perioperative insulin sensitivity with administration of maltodextrin, as well as a reduction in postoperative gluconeogenesis, which together improve postoperative glucose metabolism for as long as 72 hours postoperatively. However, the recent data from the PROCY trial suggest that the delivery of the recommended 3 doses of 40+ g of maltodextrin per dose does not sufficiently reduce the population rate of hyperglycemia (25% range) to decrease perioperative complications. However, a strategy of administering 3 doses of 25 g provided similar benefits, with a perioperative hyperglycemia rate of 7%.

The preoperative loading period also allows for the opportunity to support
a recently documented impact of surgical stress on the reduction of arginine bioavailability and an associated increase in asymmetric dimethyl arginine (ADMA), which is a natural inhibitor of arginine-associated nitric oxide function.\textsuperscript{82-84} The net result is a lowering of the arginine/ADMA ratio in the early postoperative period, which is associated with increased SSI rates, cardiovascular complications, and acute kidney injury.\textsuperscript{85,86} Both Ekeloef et al\textsuperscript{87} and Ragina et al\textsuperscript{88} recently demonstrated a significant reduction (20%-25%) of both arginine and endothelial function after colectomy. L-citrulline has recently and consistently been demonstrated to safely and effectively restore systemic arginine levels and reduce ADMA in a variety of clinical scenarios. The major reason for reliance upon citrulline is that surgical stress increases the function of constitutively active hepatic arginase, which degrades a significant component of enterally administered arginine, rendering it inactive.\textsuperscript{89-91} Conversely, virtually all enterally absorbed citrulline passes through the liver to subsequently be converted virtually completely to arginine in the kidney. The net result is that citrulline directly supports systemic access to arginine for use by all end organs and immune response cells (ie, macrophages and lymphocytes).\textsuperscript{92-94} The higher degree of bioavailability of systemic arginine is also important because of its ultimate conversion to ornithine and then proline, which supports wound healing via collagen formation. Higher doses of arginine required to support similar systemic levels are limited by the GI side effects on small bowel secretion of fluid and electrolytes.\textsuperscript{92-94} Therefore, the preoperative “loading” period may need to be further investigated to allow support of important aspects of both glycemic management and endothelial function.

**BOWEL PREPARATION (COLON RESECTION ONLY)**

The classic article by Condon et al\textsuperscript{95} assessed bowel preparation strategies in a 3-arm study comparing intravenous cephalothin alone versus oral neomycin and erythromycin alone versus both intravenous and oral regimens. This 3-arm trial showed superior outcome in the dual regimen; however, the intravenous medication was limited in bacterial coverage, which may have impacted the results. This issue was addressed by Coppa and Eng,\textsuperscript{96} with 350 patients randomized to intravenous cefoxitin with or without oral neomycin and erythromycin. They found significant improvement as well with dual regimens for wound infection (11% vs 5%). As a result of that work and
other work, including the seminal work of Nichols and Condon, MBP including oral antibiotics supplemented with preoperative intravenous antibiotics has been a mainstay of colon surgery for decades. MBP has been primarily associated with reductions in SSI, especially superficial wound infection, although more recently, it has been associated with a reduction in anastomotic leak. However, in the ERP era, the utility of MBP has been questioned by 2 meta-analyses evaluating recent data. The meta-analysis by Bucher et al included 7 RCTs available in the literature and suggested a higher incidence of anastomotic dehiscence in patients receiving MBP (5.6%, 36/642 patients) versus no MBP (2.8%, 18/655 patients; $P = .03$; odds ratio [OR], 1.85; 95% confidence interval [CI], 1.06-3.22). The rate of intra-abdominal infection (peritonitis or abscess) was similar in the MBP group (3.7%, 17/458 patients) compared with the no-MBP group (2.0%, 9/461 patients; OR, 1.69; 95% CI, 0.76-3.75; $P = .18$). The rate of wound infection was not significantly different in patients receiving MBP (7.5%, 48/642 patients) versus no MBP (5.5%, 36/655 patients; OR, 1.38; 95% CI, 0.89-2.15; $P = .15$). The meta-analysis is significantly impacted by 2 studies. The first is by Contant et al that studied 1431 patients undergoing open colorectal resection randomized to intravenous antibiotics (aerobic and anaerobic coverage) with or without MBP. The data demonstrated a significant increase in the rate of intra-abdominal abscess (2.5% vs 0.3%); however, there was no significant difference in superficial wound infection (no MBP vs MBP, 14% vs 13.8%) or anastomotic leak (no MBP vs MBP, 5.4% vs 4.8%). The authors concluded that MBP can be safely avoided. However, the increase in pelvic abscess rate and a fairly high superficial wound infection raise some concern over this recommendation and possibly the negative impact of no oral antibiotics. Jung et al performed a similarly designed study of 1505 open colectomy patients and also concluded that there was no significant difference in wound infection (MBP vs no MBP, 7.8% vs 6.4%) or anastomotic leak (MBP vs no MBP, 2% vs 2.6%). A major pitfall of these combined data is the absence of the putative effective treatment that incorporates oral antibiotics with the MBP.

In recent years, many papers have reviewed large quality databases, and the consistent theme seems to be a significant reduction in both SSIs and anastomotic leaks. The Michigan Surgical Quality Consortium
analyzed 2062 elective colectomies between January 2008 and June 2009; 49.6% of patients were administered MBP and 36.4% received MBP and oral antibiotics. Patients receiving oral antibiotics were less likely to have any SSI (4.5% vs 11.8%; \( P = .0001 \)), to have an organ space infection (1.8% vs 4.2%; \( P = .044 \)), and to have a superficial SSI (2.6% vs 7.6%; \( P = .001 \)). \(^{102}\) Patients receiving bowel preparation with oral antibiotics were also less likely to have a prolonged ileus (3.9% vs 8.6%; \( P = .011 \)). Similarly, Kiran et al\(^{103}\) reviewed the National Surgical Quality Improvement Program–targeted colectomy data initiated in 2012 to capture information on the use and type of bowel preparation and colorectal-specific complications. They found that in 8442 patients, MBP with antibiotics, but not without, was independently associated with reduced anastomotic leak (OR, 0.57; 95% CI, 0.35-0.94), SSI (OR, 0.40; 95% CI, 0.31-0.53), and POI (OR, 0.71; 95% CI, 0.56-0.90). \(^{103}\) A recent meta-analysis and a review of the older prospective randomized trials came to the same conclusion based on high-quality studies. \(^{108,113}\) Finally, Wick et al\(^{109}\) described the incremental benefit of adding an MBP with oral antibiotics to their ERP with significant reductions in SSI. Therefore, despite the recommendations of the ERAS Society and in the absence of any convincing data from their data set or a well-powered study comparing no preparation to MBP with oral antibiotics, this author recommends the latter strategy as part of an effective ERP.

PREOPERATIVE EDUCATION

The importance of providing consistent, precise, and easily understood information regarding the episode is key to developing an effective ERP. \(^{114-116}\) It is beyond the scope of this chapter to define specifics because the goal of the educational program needs to be both patient centric and system specific. It goes without saying that in order to provide high-quality care and allow a pathway for the patient to be an effective member of the team it is essential that everyone agrees to the components of care. Patients are highly sensitive to variations in messaging, and failure in consistently messaging the processes and goals can render an ERP ineffective.

Day of Surgery
The Surgical Care Improvement Project (SCIP) program campaign began in August 2005 as a mandated national initiative with public reporting of compliance designed to primarily reduce the risk of SSI. There has been considerable debate on the relative benefits of various components, or even the degree of compliance on outcomes related to institutional adoption of the SCIP, and ultimately, the program was retired in December 2015. With respect to ERP, the important process measures that seem to be highly effective and that should be adhered to include selection of an appropriate parenteral antibiotic; administration of that antibiotic within 1 hour preoperatively; termination of the antibiotic prophylaxis within 24 hours of surgery; removal of the urinary catheter within 24 hours; and appropriate deep venous thrombosis prophylaxis.

**ILEUS PROPHYLAXIS**

POI had traditionally been perceived as an unavoidable outcome of major abdominal surgery, primarily due to poorly understood multifactorial pathophysiology. Although POI is frequently blamed on factors out of the control of the surgeon, including neurogenic stimuli, release of inflammatory mediators, or requisite surgical manipulation, it has become clear that the majority of the cause is related to narcotic analgesics. Surgery-related mediators also cause the release of endogenous opioid peptides that further exacerbate the effects of exogenous opioid analgesics (administered for analgesia) on the inhibition of bowel function. POI occurs at a lower rate following minimally invasive surgical procedures due to a reduction in surgical trauma and postoperative pain but may still occur due to the effects of opioid analgesics. Although not life-threatening, POI prolongs postoperative hospital stay and healthcare resource utilization and costs. Therefore, without a reduction in POI, an ERP will be unsuccessful in safely reducing the hospital stay and potentially the readmission rate. Although a narcotic-sparing analgesic regimen (see later in this chapter) can minimize the risk of POI, the availability of alvimopan, a first-in-class oral μ-opioid receptor antagonist, offers the only prophylactic treatment that reduces the rate of POI. A pooled analysis of the phase III prospective,
randomized, and blinded alvimopan trials confirmed that a 12-mg dose provided optimal reduction in GI morbidity and return of GI function.\textsuperscript{135} Subsequent to the prospective randomized trials, several large quality databases have been interrogated and confirmed the system-level benefits of a strategy of POI prophylaxis that incorporates alvimopan in the care plan.\textsuperscript{23,136-139} Gum chewing has been advocated as another option to reduce the rate of POI; however, in a program employing early feeding strategies, the relative benefits of chewing gum remain unclear, but it is inexpensive and apparently safe.\textsuperscript{140,141}

**NAUSEA AND VOMITING PROPHYLAXIS**

Postoperative nausea and vomiting (PONV) are common and unpleasant side effects associated with anesthesia and surgery, with an incidence of approximately 30%.\textsuperscript{1} High-risk patients may have a considerably higher incidence, especially females, nonsmokers, patients with a history of motion sickness or migraines, and patients exposed to narcotics or volatile anesthetics.\textsuperscript{142,143} Current therapeutic options include a combination of antiemetics acting at different receptors.\textsuperscript{144} The major receptor systems are involved in PONV including the cholinergic (muscarinic), dopaminergic (D\textsubscript{2}), and histaminergic systems. Ondansetron, granisetron, dolasetron, and tropisetron have shown efficacy for PONV prevention and are associated with a low incidence of side effects. Metoclopramide acts on both central dopamine and serotonin receptors and has both prokinetic and antiemetic effects but may be limited due to extrapyramidal side effects. Dexamethasone is an effective antiemetic, although its mechanism of action remains uncertain.\textsuperscript{144} Based on current evidence, a multimodal approach to PONV should include the following strategy: (1) preoperative anxiolysis; (2) aggressive hydration (25 mL/kg) in outpatients unclear of impact in guided fluid management for major surgery; (3) oxygen; (4) prophylactic antiemetics (dexamethasone 10 mg at induction and ondansetron 1 mg at end of surgery); (5) total intravenous anesthesia with propofol, remifentanil, and a nonsteroidal anti-inflammatory drug; and (6) avoidance of nitrous oxide.\textsuperscript{145,146}

TRANSVERSUS ABDOMINIS PLANE BLOCK FOR
ANALGESIA

The initial description of the landmark technique for performing transversus abdominis plane (TAP) block advocated a single entry point, the triangle of Petit, to access a number of abdominal wall nerves, hence providing more widespread analgesia.\(^{147,148}\) Ultrasound guidance was subsequently recommended to improve localization and deposition of the local anesthetic and was associated with a sensory block from T7 to L1.\(^{149}\) Radiologic evidence suggests that 20 mL of dye in the TAP 20 to 240 minutes after injection migrated from the superior margin of the iliac crest to the level of the costal margin and posteriorly to the quadratus lumborum.\(^{149}\) The “4-quadrant TAP block” is a further enhancement of analgesia and is beneficial due to analgesic impact to both the intercostal (upper TAP) plexi and the deep circumflex iliac artery plexi (lower TAP plexus).\(^{150,151}\) Although data are pending from several ongoing trials, a 4-quadrant block appears to be a safe and inexpensive adjunct to an effective narcotic-sparing analgesia. This is supported by a variety of large data set analyses as well as a single-institution experience within an otherwise unchanged ERP.\(^{152-158}\)

EPIDURAL ANESTHESIA AND ANALGESIA

Epidural anesthesia as a component of ERP originated from the early work of Henrik Kehlet and his team, who investigated the potential benefits of reduction of the perioperative stress response.\(^{159,160}\) Interestingly, unlike many of the subsequent analyses of ERP components by this team, it remained untested in randomized studies. As a result, it remains a component of recommendations of the ERAS Society (http://erassociety.org/guidelines/list-of-guidelines/). However, the growing understanding and adoption of various narcotic-sparing strategies have generally reduced the impact of epidural analgesia within an ERP. The majority of recent studies, especially in laparoscopic colorectal surgery, have identified limited adjunctive analgesia benefits.\(^{161-166}\)

GUIDED FLUID MANAGEMENT

The title of this section was purposely changed to “guided” rather than “goal-directed” to attempt to refine the direction the therapeutic management of
perioperative fluid appears to be heading. The current discussion includes *liberal versus restrictive* and *goal directed* as the 2 main approaches to particularly intraoperative fluid management. Conversely, the concept of “guided” offers a middle ground of fluid administration based on additional assessments identifying patients who may or may not be fluid responsive. The latter may benefit from a strategy of judicious pressor therapy for hypotension or inotropic support for impaired myocardial contractility.²⁰,²¹

A report from the United Kingdom in 1999 identified that fluid imbalance led to serious postoperative morbidity and mortality and was associated with a high frequency of poor documentation of fluid balance.²²,²³ That same report suggested that overhydration was a contributory cause of postoperative morbidity and mortality.²² Both hypervolemia and hypovolemia impair cardiac function, pulmonary function, tissue oxygenation, wound healing, POI, renal function, and coagulation, which may all be affected by perioperative fluid administration.²⁴ Therefore, the true relationship between postoperative complications and volume loading is a U-shaped curve with the goal being lower on either arm of the U.²⁵

The traditional approach to fluid therapy includes replacement of the fluid lost (by basal fluid requirements, perspiration through the surgical wound, loss to the third space and blood loss, and exudation through the surgical wound) and maintenance of physiologic functions (preloading of neuraxial blockade).²⁶ This approach has been associated with high volumes manifested by postoperative weight gain. Alternatively, restricted fluid therapy is based on a mL/kg/h strategy that seeks to achieve a zero balance.²⁶ The data have clearly demonstrated that a liberal versus restrictive fluid management is consistently associated with a greater incidence of major postoperative complications.²⁷ However, there is an often underappreciated complication rate associated with underresuscitation, primarily manifested by acute kidney injury.²⁷ Therefore, a recent critical analysis of the available studies reported that 3 of the trials showed improved outcome after restrictive fluid regimens; 2 trials showed no difference in the outcome.²⁸

Goal-directed fluid management strategies have become popular and rely on one or another means of optimizing cardiac output; however, the data on relative benefits of supranormal cardiac output remain elusive.²⁹ Therefore, this approach is rapidly morphing into a concept of guided or individualized fluid administration, primarily based on an assessment of fluid
responsiveness. The appropriate identification of fluid responsiveness under general anesthesia and mechanical ventilation requires a dynamic parameter of cardiac function. The current methodologies include indicators derived from pulse power analysis, pulse contour analysis, esophageal Doppler monitoring, and others. Esophageal Doppler uses a thin plastic tube placed in the esophagus to calculate cardiac output based on the amount of blood that moves past the probe over a given time (stroke distance) and estimates the cross-sectional area of the aorta determined from nomograms. Fluid responsiveness is then implied by changes in stroke volume. A typical strategy uses an increase in stroke volume of at least 10% by a fluid bolus of 3 mL/kg, as consistent with fluid responsive, and the boluses continue until that 10% increase is reached. Alternatively, arterial pulse contour analysis measures the stroke volume on a beat-to-beat basis from an arterial pulse waveform, but the main drawback of this method is that it is an invasive procedure. Respiratory variations in the arterial pulse pressure in patients on positive-pressure ventilation can inform clinicians about the status of a patient on the Frank-Starling relationship. High respiratory variations (>15%) mean that the patient is on the steep portion of the curve, and low respiratory variations (<10%) indicate that the patient is on the plateau (ie, not fluid responsive). A similar strategy of boluses can be administered until the plateau is reached. The specific fluid remains controversial, with recommendations for colloid or balanced crystalloid as the predominant solutions.

**Postadmission**

**NARCOTIC-SPARING ANALGESIA**

Effective analgesia with minimal side effects is one of the most important components of ERPs and, when fully adopted, results in high-quality and high-value surgical care. The same care plans can be adopted for a broad range of GI surgeries, but a transition in a conceptual approach to analgesia is required. We need to continue to separate ourselves from the concepts of the 1990s when regulatory agencies such as The Joint Commission identified pain as the “fifth vital sign” and the Centers for Medicare and Medicaid Services included satisfaction with analgesia as a quality reporting
The result was a tremendous increase in the use of narcotics, and unfortunately, a narcotic epidemic has occurred, with unintentional drug overdose now the second leading cause of accidental death. Evolving acute pain management from the various forms of the World Health Organization “analgesic ladder” to the concepts of (1) TAP block/neuraxial block; (2) scheduled narcotic-sparing multimodal oral analgesia (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen, and gabapentin); (3) oral narcotic for initial breakthrough pain; and (4) reservation of parenteral narcotics for severe residual pain. The increasingly limited use of epidurals for the majority of ERP GI surgery indications has been mentioned earlier. In addition, the field of pharmacogenetics has yielded preliminary data regarding the ability to significantly reduce the amount of narcotics and treatment-related pain scores by using patient-centric optimally metabolized medications.

As mentioned earlier, an oral, scheduled, multimodal analgesic plan is a key construct of ERP analgesia. NSAIDs are potent analgesics (600 mg of ibuprofen is as efficacious as 15 mg of oxycodone hydrochloride) and act through inhibition of cyclooxygenase and prostaglandin synthesis. The addition of NSAIDs (including nonselective and cyclooxygenase-2 inhibitors) has clearly and consistently been tied to superior analgesia and opioid-sparing effects. NSAID administration has been associated with platelet dysfunction, GI tract irritation or bleeding, and renal dysfunction. A Cochrane review that examined 23 trials (comprising 1459 patients) noted that NSAIDs caused a clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function and should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment. Conversely, the perceived risk of NSAID-related increases in postoperative bleeding has been refuted by a significant amount of data. There has been growing concern regarding NSAID-related anastomotic leak, which has been suggested in several reports. Some data suggest an association between NSAID use and an increase in anastomotic leakage; however, further studies are needed to determine the validity of this association. There is some literature suggesting that variable systemic levels can occur in patients with mutations in the CYP2C8 or CYP2C9 genes, which can result in delayed metabolism and therefore supratherapeutic drug
Therefore, utilization of naproxen, which is one of the few NSAIDs (selective or nonselective) that is excreted unchanged in the urine and therefore not impacted by genetic variation, may offer a safer strategy.

Acetaminophen is available in both oral and parenteral forms and should also be provided in a scheduled fashion within an ERP. The recurring theme is improved analgesia, narcotic reduction, and reduced opioid side effects. Although theoretically tied to hepatic toxicity, the risk is minimal when acetaminophen is administered in the usually recommended dosage range, which yields an additive analgesic benefit to concomitant NSAID use.

Gabapentinoids (gabapentin and pregabalin) are another synergistic component of the multimodal analgesic program. Gabapentin potentially acts to produce its pain-relieving effects by (1) inhibition of injury-induced spinal neuronal excitability, evoked hypersensitivity, and ongoing pain and (2) selective supraspinal modulation of affective qualities of pain, without alteration of reflexive behaviors. Once again, robust meta-analyses indicate that a gabapentin or pregabalin administered preoperatively is associated with a decrease in postoperative pain and opioid consumption. Gabapentinoids may be associated with adverse effects, including sedation, dizziness, and peripheral edema, and therefore, dose modification may be required during therapy, especially in the elderly.

Judicious use of narcotics may still be required for effective analgesia, and narcotics do not need to be withheld if used in the background of the narcotic-sparing regimen. There are robust data regarding potential benefits of intravenous narcotics administered via a patient-controlled delivery system versus epidural or other analgesic strategies, especially in conjunction with novel agents such as dexmedetomidine, which has shifted the focus back to an intravenous strategy. The nuances of analgesic treatment by GI surgery discipline will be discussed in other chapters.

**EARLY FEEDING**

Amazingly, early offering of food based on patient tolerance remains one of the more difficult components of ERP to implement as a result of persisting biases of much of the care team, including both nursing and surgery. In fact, the concept of early feeding safety was a product of the introduction of laparoscopic colectomy and existed prior to the actual introduction of ERP
Laparoscopy raised questions regarding the long-held dogma of NPO until return of bowel function. This concept was then appropriated by the ERP movement and is routinely recommended for ERP across all GI surgical procedures. Optimal implementation occurs with implementation of the PONV and POI prevention strategies, as well as effective narcotic-sparing analgesic regimens. A common misconception is that intolerance of early feeding is not a cause of POI but rather the harbinger of the onset of POI.

**EARLY AMBULATION**

Early ambulation after surgery is another easily understood but difficult to implement strategy within ERP, primarily related to the reliance upon nurses who have multiple other patient care obligations. In addition, there may be physical limitations of the nurse that may limit the ability to manage a larger, unsteady patient. The concept is not new, as evidenced by the work of Canavarro in 1946 who recognized the value of early postoperative ambulation. Although the concept is advocated in virtually all published ERPs, the growing acceptance of mobility programs will likely be the component of care most likely to lead to successful implementation of the strategy. Many institutions have implemented similar low-cost programs, relying on specially trained medical aides to assist patients to safely ambulate. Once again, effective narcotic-sparing analgesia that reduces the side effects of medications that can cause dizziness or unsteadiness are adjunctive to the process. In addition, early removal of urinary catheters and intravenous lines allows the patient to ambulate without being encumbered.

**ERP SPECIFICS BY GI SURGICAL DISCIPLINE**

**Esophagectomy**

The components of ERP for esophagectomy remain highly variable, but commonly accepted components seem to be epidural for postoperative analgesia, supplemental enteral nutrition, and active physiotherapist involvement to facilitate early postoperative mobilization. Conversely, there appears to be little consensus on the use of drains, use of nasogastric tubes,
time taken to commence oral intake, and use of postoperative oral contrast studies.\textsuperscript{223-225} The confusion lies mainly with the fact that there is limited robust, high-grade evidence for many of the elements within ERP.\textsuperscript{224,225} One facet that seems to be clear is that early enteral nutrition is superior to the use of total parenteral nutrition, with consistently lower septic complications associated with some form of enteral nutrition.\textsuperscript{226,227} Various tube feedings (jejunostomy vs nasojejunal) have been assessed and offer effective means of feeding delivery with a low incidence but different set of tube-related complications. The timing of early oral intake after esophagectomy remains poorly evaluated, with some studies suggesting safety and a reduced length of stay, while others have suggested superior outcomes with prolonged use of tube-based enteral feeds.\textsuperscript{228-232} Similarly, although not robust data, it appears that there is limited need for nasogastric decompression after esophagectomy, which improves patient comfort with increased risk of complications.\textsuperscript{233,234} As a result of these data, it appears that virtually all of the components of ERP discussed earlier in the chapter apply to esophagectomy; however, experts in the field should focus on the optimal strategy for enteral nutrition and timing for resumption of oral intake.

**Gastrectomy**

A recent systematic review and meta-analysis reviewed the highest quality data available for gastrectomy ERP, which consisted of 14 studies.\textsuperscript{235} Although the authors identified highly disparate ERPs across the studies, most of the earlier mentioned processes of care were used. Once again, limited use of nasogastric tubes and early resumption of oral intake appear safe and feasible. They also identified that ERP was associated with reduced serum inflammatory response (C-reactive protein: standardized mean difference [SMD], 0.68 [95% CI, 1.16-0.19], \( P = .007 \); interleukin-6: SMD, 0.62 [95% CI, 0.94-0.29], \( P < .001 \)), less weight loss (SMD, 0.79 [95% CI, 1.11-0.46], \( P < .001 \)), and lower cost (SMD, 1.02 [95% CI, 1.59-0.45], \( P < .001 \)), and no increase in postoperative morbidity (OR, 0.83 [95% CI, 0.65-1.06], \( P = .13 \)) or hospital readmission (OR, 1.67 [95% CI, 0.88-3.19], \( P = .12 \)).\textsuperscript{235} Better identification of gastrectomy-specific differences in complications may allow better tailoring of a specific ERP.
Hepatectomy

Hughes et al\textsuperscript{236} performed a meta-analysis of studies assessing hepatectomy ERP and determined that basically all the elements associated with colectomy (with clear support for no bowel preparation) were safe and effective. Two areas of opportunity appear to be specific to hepatectomy: (1) optimal fluid management intraoperatively and (2) the necessity of epidural for analgesia. Clearly, using strategies to reduce intraoperative blood loss are important to reduce liver-specific surgical complications, especially reducing intraoperative central venous pressure and possibly acute normovolemic hemodilution.\textsuperscript{237-239} Similarly, as is true in other GI surgical areas, the role of epidurals has been questioned and may actually impair recovery.\textsuperscript{240,241}

Pancreatectomy

Xiong et al\textsuperscript{242} performed a meta-analysis of the available high-quality but limited data (14 studies) related to pancreatectomy. Discussions regarding the nuances of gland management, anastomotic technique, and drain management are beyond the scope of this chapter and not properly part of ERP. Again, the elements are variably implemented, but the majority of the process measures are useful in pancreatectomy. The benefits of implementation of an ERP include reduced length of stay (weighted mean difference, –4.17 days; 95% CI, –5.72 to –2.61 days), reduced delayed gastric emptying (OR, 0.56; 95% CI, 0.44-0.71), reduced overall morbidity (OR, 0.63; 95% CI, 0.54-0.74), and reduced in-hospital costs compared with conventional perioperative care (all $P < .001$).\textsuperscript{242} Implementation of an ERP appears safe and will yield incremental improvement compared to standard care in pancreatectomy.

THE BUSINESS CASE FOR ERPs

As the US healthcare system moves toward the concept of value-based purchasing, it is likely that some form of “bundled care” payment structure for GI surgery will be implemented and will demand a precise understanding of the cost and quality of care within a provider group. An example of the type of institutional-level economic data that are helpful is demonstrated by
the use of submitted billing information, as described by Asgeirsson et al.\textsuperscript{243} These data identified the system-level “best case” economic outcome and defined clinical cost drivers for the most frequent variances to guide quality improvement. As an example, open colectomy was associated with higher cost compared with laparoscopic colectomy; however, the only team discussion was a frequent review to assure that use of minimally invasive techniques were used when indicated. Clearly, this “perfect outcome” is a combination of high-quality patient-centric outcomes, short length of stay, appropriate resource consumption, and reduction of complications and readmissions. This is often misconstrued as the mere presence of variation of care rather than a full discussion of patient-centric versus provider-centric outcomes, as well as necessary and unnecessary variations in care. This type of rigorous analysis demands a keen understanding of the evidence-based and cost-effective strategies that must be used by the team, not as a cookie cutter approach to care. The patient-centric approach often is confused with the need for risk adjustment, and although not every patient is set up for a similar outcome, the care plans for the primary disease and associated comorbidities can be anticipated and standardized. An example of this type of understanding is the concept of “diagnosis-related group migration,” which is defined as a patient admitted without any comorbidities who develops postadmission complications.\textsuperscript{244} This is also a simple analytic approach for a US institution to implement because the data are reported for claim submission and represent either an honest assessment of current performance or an opportunity for improved documentation and coding. Although some process for assessing and communicating risk-adjusted outcomes is necessary for intra-institution and cross-institution cost and quality comparisons, there has been a failure to clearly articulate processes of care that are effective in delivering complication reduction and the remaining “acceptable” level of these occurrences using statistical process control or equivalent methodology.\textsuperscript{245,246}

Fry et al\textsuperscript{247,248} presented a system that was based on readily available administrative data that can accurately monetize the cost of a deliverable episode of care for a given provider. An equally precise and yet easy to calculate system is the Hospital Stay, Readmission, and Mortality Rates (HARM) score, which uses surrogate measures of length of stay, mortality, and readmissions.\textsuperscript{249,250} Gramlich et al\textsuperscript{13} provide one of the best descriptions of a system-wide implementation of ERP using the Province of Alberta,
Canada, journey. They described the many theories and potential mechanisms for change management and defined their use of the Quality Enhancement Research Initiative (QUERI) model and adoption of the Theoretical Domains Framework (TDF). Readers are referred to the Gramlich article because it provides a good background for successful implementation. It will be intriguing, based on the earlier discussions on various elements of ERP, how the team revises their care plan based on new science. For example, it remains to be determined, given the recent data regarding the role of carbohydrate loading, the expected outcome (reduced hyperglycemia), and the failure of many of the commonly recommended strategies to be effective, whether their system will provide a platform for ongoing refinement and rapid process change.

Ultimately, the reader should be left with the conclusion although components of ERP may differ, it is easy to assess progress if a process is tied to an outcome and measured. In addition, it is clear that adoption of an ERP will routinely lead to some, often significant, improvements of clinical and financial outcomes. Therefore, the Nike tag line “Just do it” seems *apropos*. A recommended set of process measures and the associated outcome measures are provided in Table 3-1.

### TABLE 3-1: ENHANCED RECOVERY PROGRAM PROCESSES OF CARE AND ASSOCIATED OUTCOMES

<table>
<thead>
<tr>
<th>Process</th>
<th>Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia evaluation</td>
<td>Blood utilization; surgical site infection; transfusion-associated complications</td>
</tr>
<tr>
<td>Patient education</td>
<td>Compliance with patient-performed care components; patient satisfaction</td>
</tr>
<tr>
<td>Assessment of nutrition/sarcopenia</td>
<td>Surgical site infection; respiratory failure/pneumonia; wound complications</td>
</tr>
<tr>
<td>Carbohydrate loading</td>
<td>Hyperglycemia rate (&gt;140 mg/dL) in nondiabetics; surgical site infection; acute kidney injury</td>
</tr>
<tr>
<td>Bowel preparation (colectomy only)</td>
<td>Surgical site infection</td>
</tr>
<tr>
<td>Surgical care improvement program components</td>
<td>Surgical site infection; urinary tract infection</td>
</tr>
<tr>
<td>Ileus prophylaxis</td>
<td>Ileus rate; increased bed days due to ileus</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting prophylaxis</td>
<td>Need for rescue therapy</td>
</tr>
<tr>
<td>Narcotic-sparing analgesia</td>
<td>Pain scores; patient satisfaction; rate of opioid-associated adverse events</td>
</tr>
<tr>
<td>Guided fluid management</td>
<td>Fluid overload–related complications; rate of acute kidney injury; need for rescue diuresis/resuscitation</td>
</tr>
<tr>
<td>Early feeding</td>
<td>Ileus rate; alteration in diet due to failure; length of stay</td>
</tr>
<tr>
<td>Early ambulation</td>
<td>Length of stay; rate of pneumonia/deep vein thrombosis; fall rate</td>
</tr>
</tbody>
</table>

REFERENCES


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INTRODUCTION

Surgeons are under enormous pressure from multiple healthcare stakeholders to measure and improve their performance. Government regulators are publicly reporting patient outcomes and satisfaction scores.\(^1\) Payers are reducing reimbursements based on quality measurements.\(^2\) Licensing boards and professional societies are revising member certification to increasingly include performance evaluation.\(^3\) Patients are now searching online for information about surgeon outcomes to guide where they seek care.\(^4\) Surgeons themselves have created quality collaboratives to share best practices and improve their own performance.\(^5,6\) In short, we are in an era of unprecedented focus on evaluating and reporting the work of surgeons.

Despite the widespread interest in measuring and improving surgical
quality, little consensus exists on what measures to follow or which strategies to implement. In this chapter, we describe the general principles of performance measurement in surgery, including how to choose among measures. We then outline the benefits and drawbacks of different performance improvement strategies.

PERFORMANCE MEASUREMENT IN SURGERY

Establishing accurate measurement of surgical quality is essential to any attempt at improving performance. The following sections describe the key principles to understanding the underlying methodology and options for performance measurement.

Understanding Variation in Outcomes

Some hospitals and surgeons seem to simply do better than others, and this reality creates an opportunity to learn and improve from the best performers. However, reliably and fairly identifying high and low performers can be challenging. In addition to the quality of care provided, patient outcomes can also be highly influenced by chance and case mix. To understand how best to measure quality, it is important first to explore why outcomes vary across hospitals and surgeons.

SAMPLE SIZE AND THE PROBLEM OF CHANCE (“JUST BAD LUCK”)

Variation in outcomes across surgeons and hospitals may be the result of good or bad luck. The role of chance becomes important in low-volume procedures (eg, pancreatectomy) or when the event rate is low (eg, death after a cholecystectomy). Good or bad luck can result in either a type 1 or type 2 error.

Type 1 errors occur when extreme outcomes—good or bad—are attributed to quality when they actually are simply due to chance. Consider, for example, the “zero-mortality paradox” observed in Medicare claims data. A hospital with a 0% mortality rate 3 years in a row for pancreatic resection
might be considered the highest quality; however, in a subsequent year, it might have a 30% higher mortality rate than other hospitals. The apparent paradox is explained by the fact that most hospitals with a 0% mortality rate simply have a low case volume and good luck, and thus, this rate does not accurately reflect the quality provided at these hospitals. In other words, the difference between a low-volume hospital (e.g., 5 pancreatectomies a year) having a 0% mortality rate (no deaths) or 20% mortality rate (1 death) is more likely due to chance rather than quality. Thus, reporting a mortality rate of either 0% or 20% does not accurately represent the quality provided at a hospital.

Type 2 errors occur when real differences in quality are difficult to detect because of limited sample size. Widely recognized in clinical trials as being “underpowered” (i.e., sample is not large enough to find differences), limited sample size is commonly overlooked in surgical quality improvement initiatives. For example, a review of quality indicators recommended by the Agency for Healthcare Quality and Research found that only a small minority of hospitals have adequate surgical volume to detect meaningful differences in mortality rates. Thus, although there may be real differences in quality between hospitals, a type 2 error prevents them from being detected.

THE ROLE OF CASE MIX (“BUT MY PATIENTS ARE SICKER”)

When presented with their own outcomes data, surgeons with worse outcomes often intuitively reply, “But my patients are sicker.” Without question, patient characteristics, including their comorbid conditions, functional status, procedure indications, and so on, play a role in patients’ outcomes and should be accounted for when measuring outcomes. How much patient characteristics matter, however, depends on the comparison being made.

Adjustment for case mix (the type or mix of patients) is most important when there are strong underlying differences in the patients being compared. For example, comparing groups of patients in 2 different surgical intensive care units should be adjusted for case mix. The age, Acute Physiology and Chronic Health Evaluation (APACHE) score, and health profiles of the patients in an intensive care unit may vary widely and contribute significantly to the variation in their outcomes. Similarly, adjusting for case mix is
appropriate when comparing the outcomes of a tertiary referral hospital (which treats many complex cases) to those of a smaller community hospital (which may only operate on generally healthier patients requiring less complex procedures).

The importance of case-mix adjustments may be overstated when making procedure-specific comparisons. For example, the unadjusted coronary artery bypass grafting (CABG) mortality rates in the state of New York in 2001 ranged from <1% to 4%. When the outcomes were risk-adjusted for patient factors, the variation remained essentially unchanged. In other words, little of the variation in mortality rates could be explained by the underlying case mix because patients who undergo CABG have a relatively similar profile. This is not meant to downplay the role of risk adjustment but only to point out that, in many cases, case mix has a much smaller role than previously thought.

**What Performance Should Be Measured? The Structure, Process, Outcomes Framework**

Described first by Donabedian in 1998, the “Structure, Process, Outcomes” model is the most common framework used for quality improvement in health care. Each category has its own benefits and limitations, which are described below in the context of surgery (Table 4-1).

**TABLE 4-1: APPROACHES TO MEASURING PERFORMANCE IN SURGERY: STRUCTURE, PROCESS, OUTCOMES**
STRUCTURE

Structure refers to measurable attributes of a surgeon (e.g., years of training, specialty service availability) or hospital (e.g., number of inpatient beds, procedure volume). The primary benefit of this approach is that the data are easily collectable. Studies that described the association of better pancreas surgery outcomes with high-volume centers used this approach. Although the structure approach does well to predict outcomes across hospitals, it provides little actionable information within a hospital or about individual providers.

PROCESS

Process describes the measurable steps involved in the patient’s care. Performing certain process measures should translate to improved patient outcomes (e.g., giving preoperative heparin to reduce risk of a postoperative thromboembolism). Administrators are particularly drawn to these measures because they are readily actionable and measurable. Despite the anticipated benefit, very few “high-yield” process measures have been identified to correlate with improved patient outcomes.

OUTCOMES

Outcomes represent the end result of care. In surgery, the most common outcomes of interest are mortality and postoperative complications. These tend to have the most face validity with surgeons who often care most about
the “bottom line.” Unfortunately, comparing outcomes fairly requires high case volume (which many hospitals or individuals do not have) and detailed patient information to appropriately risk adjust. For example, comparing a process measure between 2 hospitals may only require, for example, the percentage of patients who appropriately received heparin before surgery. However, to compare the outcome (eg, rates of thromboembolism), one would need not only data on the outcome but also data on known risk factors (eg, obesity, physical inactivity, history of thromboembolism) to allow for risk adjustment and fairer comparisons. Thus, more data (and, therefore, often more resources) are required to compare outcomes performance.

**Choosing the Right Measurement Approach**

With limited resources to collect data, it can be challenging to choose where efforts should be focused. Should a surgeon be evaluated based on process measures such preoperative antibiotic administration? Or should we instead focus on the “bottom line” of the outcomes and assess surgical site infection rates? Although there are judgment calls about which should be valued over the other, there are also real statistical limitations that should help inform the choice.

Choosing the right measure will depend on the characteristics of the procedure and our ability to find meaningful differences. Statistically speaking, the more often something occurs, the easier it is to detect. Therefore, one should ask the following 2 questions: (1) How often is the procedure performed? (2) How often does the adverse event occur? Consider the following 4 categories and when structure, process, or outcomes would be an appropriate measurement approach (Fig. 4-1).\(^\text{11}\)
1. **HIGH-VOLUME, HIGH-RISK PROCEDURES SHOULD BE APPROACHED USING OUTCOMES MEASURES**

Examples of high-volume procedures with higher adverse event rates include colectomy and gastric bypass. Because they are performed fairly often and adverse events are fairly common (eg, surgical site infections after colectomy are as high as 30%), there is enough statistical power to find meaningful differences in outcomes. Although there may be a large enough case volume to look at a process measure, such as preoperative antibiotic administration, the adverse outcomes occur more frequently and would be more efficient to detect.

2. **HIGH-VOLUME, LOW-RISK PROCEDURES SHOULD BE APPROACHED USING PROCESS MEASURES**
Consider a high-volume procedure with a low adverse event rate, such as an inguinal hernia repair. Measuring an outcome such as mortality would not be helpful because it almost never occurs, even with a high case load. Alternatively, if we focus on a process measure (eg, appropriate use of preoperative antibiotics), we are much more likely to find a difference in rates between providers or hospitals.

3. **LOW-VOLUME, HIGH-RISK PROCEDURES SHOULD BE APPROACHED WITH STRUCTURE MEASURES**

When a procedure is low volume with a high adverse event rate (eg, esophagectomy), neither outcomes nor process measures make sense statistically to find differences in quality. Instead, focusing on a structure approach has been shown empirically to be the best predictor of future performance.\(^{12}\)

4. **LOW-VOLUME, LOW-RISK PROCEDURES SHOULD BE LOW PRIORITY FOR QUALITY MEASUREMENT**

Finally, limited priority should be given to operations that are low volume and low risk (eg, Spigelian hernia repair). Efforts to evaluate these procedures are lower yield than the previously described categories.

**Special Considerations When Measuring Outcomes**

Of the 3 types of measures (structure, process, and outcomes), measuring outcomes is perhaps the most challenging. As mentioned earlier, advanced statistical modeling techniques are needed when assessing outcomes to account for small sample sizes and imbalances in patient risk. Increasing progress is being made in our ability to address these limitations.

**SMALL SAMPLE SIZE CAN BE ADDRESSED WITH RELIABILITY ADJUSTMENT**

Because many hospitals individually may have lower volume, it can be difficult to determine if their outcomes truly reflect their performance or are due to “statistical noise” (ie, chance). Reliability adjustments attempts to
address this by averaging the individual hospital outcomes rate with the outcomes rate of all the hospitals combined in a weighted fashion based on volume. For hospitals with higher volume, more weight is placed on the individual hospital than the overall rate. Conversely, lower volume hospitals have less weight placed on the individual rate and more placed on the overall rate. This results in “shrinkage” of the variation displayed, and lower volume hospitals move closer to the population mean. In a sense, this gives hospitals or surgeons the benefit of the doubt of performing “average” until they have enough volume to stratify themselves as a high or low outlier. One advantage of this approach is that it prevents us from prematurely labeling high or low outliers unfairly. On the other hand, depending on the adjustment threshold used, it may prevent us from seeing differences that actually exist.

CASE MIX CAN BE ACCOUNTED FOR WITH RISK ADJUSTMENT

Accounting for case mix is important to understanding the variation in patient outcomes. How much “adjustment” is necessary continues to be refined. For example, when comparing patients undergoing a similar procedure who are likely more homogenous, a model may only need a few adjustment variables (eg, age, sex, race). Conversely, comparison across hospitals that perform different procedures may require more adjustment variables (eg, age, sex, race, operation type, admission type). Although previous models have used as many 21 variables in their risk adjustments, when making only procedure-specific comparisons, similar results can be obtained with just 5 variables. Our ability to find more efficient modeling strategies such as these will help reduce the burden of future data collection.

STRATEGIES FOR IMPROVING PERFORMANCE IN SURGERY

With accurate measurement in place, how can we improve performance? Incentives are rapidly increasing to implement strategies for improving care. The largest payer in the United States, the Centers for Medicare and Medicaid Services, established a Linking Quality to Payment initiative whereby providers are reimbursed based on specific performance measures.
Example schemes such as “pay-for-performance” and “bundled payments” have been piloted and focus specifically on surgical procedures.\textsuperscript{14,15} As payment reform continues to move toward rewarding better quality, surgeon leaders will be expected to initiate and understand quality improvement programs. In the following sections, we describe the benefits and drawbacks of the most common strategies (Table 4-2).

**TABLE 4-2: ADVANTAGES AND DISADVANTAGES OF DIFFERENT PERFORMANCE IMPROVEMENT STRATEGIES FOR SURGERY**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Examples</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public reporting</td>
<td>Hospital Compare website</td>
<td>Influences hospital administration</td>
<td>Controversial “fairness” of methodology</td>
</tr>
<tr>
<td></td>
<td>ProPublica Scorecard</td>
<td>Incentivizes hospital improvements to attract patients</td>
<td>Unclear if actually influences patients’ location of care decisions</td>
</tr>
<tr>
<td></td>
<td>Cardiac surgery in New York</td>
<td></td>
<td>Could encourage “gaming” to avoid higher-risk patients</td>
</tr>
<tr>
<td>Selective referral</td>
<td>Bariatric centers of excellence</td>
<td>Improved outcomes for complex operations</td>
<td>May limit access for minority and rural patient populations</td>
</tr>
<tr>
<td></td>
<td>Hospital network regionalization</td>
<td>Maximizes surgeon and hospital expertise</td>
<td>Less benefit for common procedures</td>
</tr>
<tr>
<td>Outcomes feedback</td>
<td>American College of Surgeons</td>
<td>Rigorous methodology that is accepted by most clinicians</td>
<td>Feedback alone does not result in improvement</td>
</tr>
<tr>
<td></td>
<td>National Surgical Quality</td>
<td>Can serve as basis to evaluate different QI interventions</td>
<td>Data collection can be resource intensive and expensive</td>
</tr>
<tr>
<td></td>
<td>Improvement Program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality collaboratives</td>
<td>Michigan Surgery Quality</td>
<td>Impact individual surgeons</td>
<td>Requires high degree of social capital and buy-in</td>
</tr>
<tr>
<td></td>
<td>Collaborative</td>
<td></td>
<td>May take long time to develop</td>
</tr>
<tr>
<td></td>
<td>American Hernia Society</td>
<td>Quickly disseminate best practices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality Collaborative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Video and coaching</td>
<td>Intraoperative coaching</td>
<td>Technical ability correlations to outcomes</td>
<td>Resource intensive</td>
</tr>
<tr>
<td></td>
<td>“Postgame analysis” of surgery</td>
<td>Very granular to improve individual surgeons</td>
<td>Methodology still in its infancy</td>
</tr>
<tr>
<td></td>
<td>video</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Public Reporting**

Public reporting involves making information about hospital or surgeon quality openly available. Examples include the Centers for Medicare and Medicaid Services Hospital Compare website and the privately run ProPublica Surgeon Scorecard.\textsuperscript{1,4} A potential advantage of these programs is that patients will act like consumers and seek out the best quality care. This in turn should motivate both surgeons and hospital quality improvement teams
to attract patients. At present, there is little evidence regarding whether patients know how to interpret these data or if they even use the data to choose their location of care. In addition, surgeons have pointed out significant methodologic limitations of these reporting mechanisms.\textsuperscript{16}

Although debates about the methods and quality of public reporting continue, the response from hospitals cannot be ignored. In 1989, the state of New York was the first to publicly report mortality rates after CABG. Shortly thereafter, many hospitals with poor outcomes completely overhauled their cardiac programs by recruiting outside personnel and investing in new infrastructure.\textsuperscript{17} Similar responses from hospitals were catalyzed by the 2005 launching of the federal government’s Hospital Compare website. Indeed, much of the quality improvement infrastructure prevalent within hospitals now that we take for granted was established in response to public reporting.\textsuperscript{18} Even if the up-and-coming forms of public reporting (eg, provider reviews on Yelp or Facebook) do not influence patients, they are likely to shape how hospital administrators make quality improvement decisions.

**Selective Referral**

Selective referral means restricting patients to locations where there are dedicated resources and expertise for a specific problem. Unlike public reporting, which is simply encouraging movement to high-quality centers, selective referral is enforced by payers who will only reimburse at a chosen location. For example, the bariatric surgery coverage decision by the Centers for Medicare and Medicaid Services established in 2006 only reimbursed for bariatric procedures at “centers of excellence.”\textsuperscript{19} This approach was intended to maximize surgeon and hospital expertise to take advantage of the known association between high procedure volume and better outcomes. In the case of bariatric surgery, this strategy did not work as intended, and later studies demonstrated no benefit over institutions that were not deemed centers of excellence.\textsuperscript{20} In addition, in the case of bariatric surgery, restricting surgical care to specific centers limited access disproportionately for minority populations.\textsuperscript{21}

Although selective referral is not ideal for all procedures, it is finding its place for complex operations. Many insurers are adopting The Leapfrog
Group recommendations to restrict reimbursement for high-risk procedures (eg, esophagectomy, pancreatectomy) to centers with high volume and other specific safety standards.\textsuperscript{22} Similarly, major hospital systems that are rapidly consolidating have adopted a “volume pledge” to regionalize complex operations within their network.\textsuperscript{23} Because this approach works best for high-risk operations that have a known volume-to-outcome relationship (eg, CABG, pancreatectomy), it has little role for a majority of procedures that are common or that have low adverse event rates. Applying selective referral to low-risk procedures could also severely limit access and place unnecessary burden on patients to travel while resulting in minimal or no benefit in outcomes.

**Outcomes Feedback**

Providing hospitals and surgeons with feedback on their outcomes is the most commonly used strategy for surgical quality improvement. The largest example is the American College of Surgeons National Quality Improvement Program, which provides over 600 hospitals with outcomes data. The program allows hospitals to measure their own performance and benchmark across centers throughout the country. An advantage of this specific approach is the rigorous methodology used to report fair, validated, and risk-adjusted outcomes. A major drawback of the system, however, is the significant cost and resources required to collect the relevant data.

Although the use of outcomes feedback has been widely adopted, it faces important challenges that need to be addressed. First, participation in a feedback program alone does not lead to quality improvement.\textsuperscript{24} Hospitals with this approach in place should also be implementing other strategies such as coaching low-performing surgeons, improving safety culture within high-risk wards, benchmarking through regional collaboratives, or implementing evidence-based perioperative guidelines. It cannot be stressed enough that although measurement of performance is necessary, by itself, it is not sufficient for improvement. Second, many data collection and reporting systems are still too inefficient and place a significant resource burden on hospitals. Efforts to improve risk adjustment methodology and streamline reliable data collection should be prioritized to reduce these financial barriers to participation.
Quality Collaboratives

Quality collaboratives are groups of surgeons or hospitals that meet regularly to share data and implement best practices. Most collaboratives form around a geographic region (eg, Michigan Surgery Quality Collaborative) or a specific surgical field (eg, American Hernia Society Quality Collaborative). Effective groups rely on a shared clinical registry that captures detailed patient information and their outcomes across multiple institutions. Members identify and share effective practices through regular face-to-face meetings, site visits, and conference calls. These serve as a basis for them to develop future targeted interventions that are evaluated, adjusted, and shared in a similar fashion. This cycle of evaluation, intervention, and dissemination allows for rapid and iterative quality improvement. Because this approach is driven largely by clinicians “on the ground,” it has face validity and focuses on problems relevant to day-to-day patient care. Furthermore, by incorporating multiple hospital systems, the collaborative can benefit from a breadth of expertise that, when shared, tremendously benefits patient care.

Creating an effective quality collaborative requires a unique combination of financial and social resources. A significant amount of capital is needed to maintain a clinical registry and subsidize surgeon time outside of the operating room to participate in collaborative events. Even with supportive administrators, collaboratives often need to look for novel funding outside of their institutions. For example, the Michigan Surgery Quality Collaborative has been able to demonstrate benefits to payers by reducing complications such that they are significantly supported by both federal research grants and private insurers. Beyond financial capital, collaboratives require a significant amount of social capital among surgeons who may be from competing hospital systems. Creating a sense of community and engagement requires time to develop trust, considerable effort, and effective leadership.

Video Analysis and Coaching

The most recent addition to quality improvement strategies is the use of video technology and coaching. Unlike other approaches that focus on care before the operation (eg, process measures, checklists) or after the operation (eg, postoperative complications, failure to rescue), video coaching is focused on the operation itself. How individual surgeons execute their technical skill has
long been a “black box” not well captured in operative reports or outcomes. Recently, however, researchers have been able to use video recording to objectively measure surgeon technical skill during laparoscopic gastric bypass procedures, and they found that variation in skill correlates with patient outcomes (Fig. 4-2).

Building on this discovery, specific coaching paradigms that incorporate “postgame” video coaching by peer surgeons have been created to improve individual surgeon performance. In doing so, it has revealed a whole new range of variables (eg, handling of tissue, type of stapler, efficiency of sewing) that were previously unable to be measured.

**FIGURE 4-2** Surgeon skill and postoperative complication rates. Surgeons were evaluated using Objective Structured Assessment of Technical Skills (OSATS); those in the top quartile were identified as “high-skill surgeons” and those in the bottom quartile as “low-skill surgeons.” Complication rates after laparoscopic Roux-en-Y gastric bypass surgery were risk-adjusted and reported by surgeon skill level. All differences in this figure were significant,
Despite the enthusiasm for how video coaching could improve surgical quality, the field itself is still in its infancy. To date, only a handful of operations have been examined with this approach, and we are still waiting on long-term trials to determine whether video-based coaching can ultimately improve patient outcomes. It is likely that multiple iterations will be needed before it can be scaled up and widely implemented. Nonetheless, once matured, this area has potential to become part of credentialing and continuing education for attending surgeons. In addition, it may be a source of novel innovation for surgical technique as we gather more granular data about the highest performing surgeons.

CONCLUSION

Pressure on surgical leaders to understand and implement performance measurement and improvement programs is at an all time high. Over the past decade, a robust body of scholarly work has advanced our understanding of measurement and improvement in surgical populations. No single measurement approach or improvement strategy is best, and each surgeon, specialty, department, and hospital will need to tailor their efforts based on their goals, as discussed earlier. The pressures from patients, payers, regulators, and specialty societies will only continue to grow and will make performance improvement central to our profession.

REFERENCES

Over the past several decades, flexible endoscopy has shifted the management of numerous gastrointestinal diseases from the surgeon to the endoscopist. What had started as a diagnostic discipline has now become one of advanced therapeutic potential. The concept of performing endoscopic surgery has become a reality with the advancement of endoluminal therapies for neoplasia, gastroesophageal (GE) reflux, motility disorders like achalasia and gastroparesis, and obesity. With advanced endoscopic tools at our disposal, endoscopic therapies are increasingly used as rescue therapies as well, especially after foregut surgical interventions. This chapter will address the indications and techniques for upper and lower flexible endoscopy as well as the recent advances in interventional endoscopy.
The flexible endoscope was initially developed in 1957 as an imaging device dependent on the delivery of light and transmission of the image along multiple bundles of chemically treated glass fibers. The fiberoptic bundle is 2 to 3 mm wide and is composed of 20,000 to 40,000 individual fine glass fibers, each approximately 10 μm in diameter. When using a fiberoptic endoscope, the endoscopist views the image through the eyepiece at the instrument head, or alternatively, a video camera can be affixed to the eyepiece to transmit the image to a video monitor. The majority of endoscopes in use today are videoscopic, although in many parts of the world, fiberoptic systems are still the standard. In these videoscopic systems, the visualized image is created from reflections onto a charge coupled device (CCD), which is a chip mounted at the end of the endoscope, rather than via the fiberoptic bundles. The CCD chip has thousands of pixels (light-sensitive points), which directly increase image resolution.

In narrow-band imaging (NBI) endoscopy, filtered light is used to preferentially enhance the mucosal surface, especially the network of superficial capillaries. NBI is often combined with magnification endoscopy. Both adenomas and carcinomas have a rich network of underlying capillaries and enhance on NBI, thereby appearing dark brown against a blue-green mucosal background. The use of white light as well as NBI has enabled endoscopists to provide an immediate assessment of small colonic lesions without histopathologic evaluation. Gastric mucosal abnormalities are also differentiated by NBI with and without magnification endoscopy. NBI can also differentiate squamous from nonsquamous epithelium to help identify Barrett’s esophagus (Figs 5-1 and 5-2).
FIGURE 5-1 Standard white light versus narrow-band imaging of the distal esophagus in patients with Barrett esophagus.
FIGURE 5-2 Differentiation of the squamous and columnar mucosa is easily seen in the narrow-band image.

**Endoscope Anatomy**

Flexible endoscopes are being created in a wide variety of lengths and diameters, with an assortment of channel numbers and sizes, adjunct imaging modalities, and intrinsic and extrinsic scope mechanics for reducing scope...
looping and providing improved scope advancement.

Uniformly, the knobs for controlling manipulation of the scope tip are located on the right side of the headpiece, with an internal larger knob for upward and downward deflections and an external smaller knob that manipulates the tip to the left and right. Locks accompany each knob to hold the deflection in position when needed. The ability for greater degree of deflection of the endoscope occurs with upward rather than downward manipulations. There is no variability in deflection provided by the right-left knob. In addition to manipulation of the deflecting knobs, significant scope rotation can be achieved by torquing the endoscope, altering the endoscopist’s stance, or rotating the headpiece while inserting or withdrawing the shaft of the endoscope.

There are 2 buttons on the front of the scope headpiece responsible for tip cleaning, air insufflation, and suction. The suction channel also functions as the biopsy channel so that any endoscopic tools placed into the biopsy channel will limit the ability to suction fluids through the endoscope. A small button on the front of the handpiece above the suction button allows for freezing of the image and digital recording by pressing the image capture button on the back of the handpiece. The endoscope is held in the left hand regardless of the individual physician’s hand dominance. The internal up and downward deflection knob is controlled by the left thumb, while the air, water, and suction are controlled by the left index and middle fingers. The smaller left-right knob is usually manipulated by the right hand.

One of the challenges in modern endoscopy, especially colonoscopy, is the formation of undesired loops in the shaft of a flexible scope. Loop formation impedes expeditious and safe passage to the cecum by transmitting the force of insertion to the colon wall or mesentery rather than to forward progression. One technical advance that aims to prevent loop formation is a variable stiffness endoscope.

**Variable Stiffness Endoscopes**

Conventional colonoscopes have a static level of column strength throughout the length of the insertion tube. The column strength determines the amount of buckling of the instrument that occurs during insertion and the level of elasticity that remains during reduction of loops. Variable stiffness endoscopes permit alteration of the column strength through an adjustable
tensioning coil (Fig. 5-3). The data from studies comparing variable stiffness colonoscopes to conventional scopes are inconclusive. Some studies report faster cecal intubation using variable stiffness endoscopes with less need for adjunct maneuvers, while other similar studies report no significant differences.6,7

**FIGURE 5-3** The variable stiffness control is seen at the base of the head piece of the colonoscope.

**Endoscopic Education**

Recent mandates from the American Board of Surgery now require surgical residents to graduate with an increased number of flexible endoscopy cases (50 colonoscopies, 35 esophagogastroduodenoscopies [EGDs]). To provide this experience and to improve the overall endoscopic education of surgery
residents, a comprehensive curriculum was needed. An iteration of such a curriculum might include periodic simulation training for first-year residents, formal endoscopy rotations for junior residents, and intraoperative and advanced endoscopy for senior and chief residents.

This is now coming into effect as the Flexible Endoscopy Curriculum (FEC). This curriculum will apply to all residents completing their general surgery residency in 2018 or later. This curriculum has 5 levels that are completed as the resident progresses through the 5 clinical years of surgical residency. To complete level 5, residents have to complete and pass the Fundamentals of Endoscopic Surgery™ (FES) program offered by SAGES. It is similar to the Fundamentals of Laparoscopic Surgery (FLS) that is currently required for all residents.

Efforts to improve endoscopic training have led to the development of computer simulators for teaching endoscopic skills. Currently, simulators are available for training in flexible sigmoidoscopy, gastroscopy, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and colonoscopy.

**PATIENT ASSESSMENT, SEDATION, AND MONITORING**

**Patient Assessment**

Although both upper and lower endoscopy can be performed unsedated, the majority of patients undergoing endoscopic procedures receive agents to provide conscious sedation. Preprocedural patient risk assessment, intraprocedural cardiopulmonary monitoring, and postprocedural recovery are vital to the performance of safe and effective endoscopic interventions. Preprocedural evaluation for American Society of Anesthesiology (ASA) risk classification and Mallampati score have become standard guidelines for most endoscopy units. Elderly patients or those with preexisting cardiopulmonary conditions are at increased risk for these complications, as are those undergoing more extensive endoscopic interventions. Patients with diseases associated with the oropharynx or trachea and those with morbid obesity, sleep apnea, or neuromuscular degenerative diseases require extra
vigilance during endoscopic procedures. As bariatric surgery is being increasingly performed, so is endoscopy in those patients by surgeons. This is both for preoperative assessment and subsequently for abnormal symptoms or complications. The challenges in morbidly obese patients include a more difficult airway, sleep apnea, possible pulmonary hypertension, difficulty in bag-mask ventilation and rescue techniques, and difficulty in monitoring.

**Monitoring**

Monitoring should be performed before, during, and after the procedure by a dedicated endoscopy assistant. Signs that are routinely monitored include the patient’s level of consciousness, degree of pain, vital signs, and respiratory status. Supplemental nasal oxygen is required to decrease the frequency of desaturation during endoscopic procedures. The patient’s oxygenation status and cardiac electrical activity are also monitored by equipment throughout the procedure. It must be understood that pulse oximetry levels can rule out hypoxia, but hypoventilation and resultant hypercarbia can still go undetected. The ASA does recommend capnography if there is a positive screen for sleep apnea. In addition, external suction for clearing oropharyngeal secretions must be immediately available and within reach of the endoscopic assistant.

**Sedation**

Sedation is a drug-induced state of depressed consciousness. It provides relief of discomfort and anxiety and allows the endoscopist to focus on the procedure. It is important to become familiar with stages of sedation (Table 5-1) if one is going to be involved in administering it.

**TABLE 5-1: FOUR STAGES OF SEDATION**

```markdown
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-sedation</td>
</tr>
<tr>
<td>2</td>
<td>Sedation</td>
</tr>
<tr>
<td>3</td>
<td>Post-sedation</td>
</tr>
<tr>
<td>4</td>
<td>Recovery</td>
</tr>
</tbody>
</table>
```
Moderate sedation, formerly known as conscious sedation, is the most frequent stage for routine endoscopy. For more complex interventional procedures, deep sedation may be needed with an anesthesia provider managing the sedation because the airway may be compromised. It is easy to progress from moderate to deep sedation, and the team must be prepared for that.

The combination of narcotics (analgesia) and benzodiazepines (sedation and amnesia) is commonly used to provide sedation during endoscopic procedures.\(^\text{16}\) Although propofol has a more rapid onset and shorter half-life, its routine use during endoscopic procedures has been widely reserved for those performed in an operating room with an anesthesiologist.\(^\text{15,17,18}\) Reversal agents (antagonists) for both class of drugs are now available and should be immediately ready for delivery in patients who show signs of oversedation. Titration of medications delivered in small increments allows for the safe performance of sedated endoscopy, especially in older patients with slower circulatory distribution.

Cardiopulmonary issues are the most commonly reported complications with endoscopic procedures. These complications include aspiration, oversedation, hypotension, hypoventilation, arrhythmia, bradycardia (vasovagal), and airway obstruction. Many of the latter are associated with use of intravenous moderate (formerly “conscious”) sedation, defined as decreased consciousness associated with preservation of protective reflexes. Table 5-2 shows risk factors for adverse events. It is especially important to note that many obese patients and other with sleep apnea may not be able to have appropriate bag-mask ventilation without an oral or nasal airway in place. A long nasal trumpet is especially useful in obese patients even without bag-mask ventilation. It may be best to involve anesthesia providers if the clinical risk factors in Table 5-2 below are present.

<table>
<thead>
<tr>
<th></th>
<th>Responsiveness</th>
<th>Airway</th>
<th>Spontaneous Ventilation</th>
<th>Cardiovascular Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal sedation</td>
<td>Normal response to verbal</td>
<td>Unaffected</td>
<td>Unaffected</td>
<td>Unaffected</td>
</tr>
<tr>
<td></td>
<td>stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate sedation</td>
<td>Purposeful response to verbal</td>
<td>No intervention required</td>
<td>Adequate</td>
<td>Usually maintained</td>
</tr>
<tr>
<td></td>
<td>or tactile stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep sedation</td>
<td>Purposeful response after</td>
<td>Intervention may be</td>
<td>May be inadequate</td>
<td>Usually maintained</td>
</tr>
<tr>
<td></td>
<td>repeated or painful stimulation</td>
<td>required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>Unarousable even with painful</td>
<td>Intervention often</td>
<td>Frequently inadequate</td>
<td>May be impaired</td>
</tr>
<tr>
<td></td>
<td>stimuli</td>
<td>required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UPPER GASTROINTESTINAL ENDOSCOPY

Indications

The indications for upper gastrointestinal (UGI) endoscopy (EGD) can be divided between those for diagnosis and those to provide for potential therapy. Diagnostic EGD is used for the evaluation or surveillance of patients who present with “alarm symptoms” (Table 5-3) as do those with abnormal or inconclusive radiographic studies. Follow-up evaluations for ulcers or surveillance for patients with Barrett esophagus are also indications. Therapeutic upper endoscopic interventions include the management of bleeding, removal or ablation of premalignant or malignant lesions, management of UGI obstructions, leaks or fistulae, and the creation of enteral access for supplemental feeding or decompression. EGD indications also now

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**TABLE 5-2: POSSIBLE CLINICAL RISK FACTORS FOR GASTROENTEROLOGIST-ADMINISTERED ENDOSCOPIC SEDATION IN OBESE PATIENTS**

- American Society of Anesthesiologists Physiologic Classification of IV or V
- Sleep apnea requiring CPAP
- Previous problems with procedural sedation or anesthesia
- The use of sedatives and analgesics
- Procedures that will require deep sedation (at a minimum), such as ERCP or EUS
- Problematic or altered oropharyngeal anatomy
  - Mallampati grade III or IV
  - Dysmorphic facial features
  - Neck mass
  - Tracheal deviation
  - Micro- or retrognathia
  - Trismus
  - <3 cm mouth opening

include treatment of disorders such as achalasia and gastroparesis through intramural surgery and interventions for GE reflux disease (GERD). Endoscopic bariatric therapies are increasingly being adopted as well.

**TABLE 5-3: INDICATIONS FOR EGD (“ALARM” SYMPTOMS)**

1. Abdominal complaints not responsive to appropriate empiric therapy  
2. Weight loss  
3. Early satiety  
4. Odynophagia  
5. Dysphagia  
6. Persistent nausea and vomiting  
7. Hematemesis/melena  
8. Foreign body impaction  
9. Iron deficiency or unexplained chronic anemia

**Contraindications**

The contraindications to EGD are related to the patient’s associated comorbidities, underlying gastrointestinal disorders, or the patient’s inability to tolerate conscious sedation. Recent myocardial infarction, pneumonia, and recent foregut surgical procedure are relative contraindications for EGD, and the risks and benefits need to be weighed on an independent basis for each patient to determine appropriateness. A recent surgical anastomosis is most likely safe at any time during the postoperative period to be evaluated endoscopically, remembering that tissue strength will be weakest on postoperative days 5 to 7.

Coagulopathy secondary to thrombocytopenia, liver failure, renal failure, and exogenous use of anticoagulants and platelet-inhibiting agents are relative contraindications for a diagnostic EGD but absolute contraindications for a therapeutic intervention. Patient noncooperation and inability for a patient to be safely sedated due to high cardiopulmonary risk are also contraindications to EGD. Respiratory depression secondary to medications and inability to maintain an airway can occur in these high-risk patients. Preassessment with ASA classification and Mallampati scores will help
predict this high-risk group. Patients with suspected perforation or caustic ingestion injury should not undergo EGD unless there are plans to provide palliative therapy such as endoscopic closure or stent placement.

**Patient Preparation**

UGI endoscopy requires very little preparation other than fasting of solid food for 6 to 8 hours and liquids for 2 to 4 hours. Removable dentures and dental implants must be taken out to avoid dislodgement and aspiration during the procedure. The role of lavage in patients with bleeding is debatable, and if large-volume lavage is to be used, care must be taken to avoid aspiration, including the judicious use of endotracheal intubation. If intervention is anticipated, a recent coagulation profile and platelet count should be within safe ranges. The use of topical pharyngeal anesthetic spray is necessary in unsedated procedures in order to suppress the gag reflex and is used based on physician preference for sedated cases.

The use of prophylactic antibiotics is rarely indicated for EGD, except in the scenario of esophageal sclerotherapy, dilation, and percutaneous endoscopic gastrostomy (PEG) tube placement. Discussion with the cardiologist as to the role of antibiotics is recommended for patients with prosthetic heart valves, previous endocarditis, systemic pulmonary shunts, or recent vascular prostheses.

**Basic Endoscopic Techniques for EGD**

The forward-viewing endoscope is preferred for routine diagnostic endoscopy. It should be noted that the medial duodenal wall, at the site of the ampulla, is preferentially seen with a side-viewing endoscope. More recently, the use of small-diameter, 5-mm transnasal endoscopes has allowed for the safe performance of unsedated endoscopy.

After appropriate preprocedural patient assessment and informed consent, the patient is routinely placed in a left side down lateral decubitus position. Patients undergoing PEG procedure or other therapies requiring access to the abdominal wall are left supine. Prior to delivery of sedation, a baseline set of vitals is taken, and it is confirmed that the equipment is in proper working order and that potentially necessary endoscopic tools are readily available.
Following the slow delivery of medications, titrating the doses as needed based on the individual patient needs, the distal several centimeters of the endoscope are lubricated avoiding the actual tip of the endoscope because this will obscure the image and, even with irrigation, will make visualization difficult.

Intubation of the esophagus is best accomplished under direct vision by advancing the endoscope over the tongue, past the uvula and epiglottis, and then posterior to the arytenoid cartilages. This maneuver will impact the endoscope tip at the cricopharyngeal sphincter and allow entry into the cervical esophagus with gentle forward pressure once the patient swallows. Blind insertion with the endoscopist’s hand in the patient’s pharynx is not recommended, as this is more dangerous for both the patient and the endoscopist. However, when intraoperative endoscopy is being done in an intubated and paralyzed patient, giving the endoscope a slight bend at the tip conforming to the shape of the pharynx and pushing forward gently while giving a jaw thrust can be helpful at times but has to be done carefully and without much resistance.

Once in the cervical esophagus, the instrument is advanced under direct vision, taking care to survey the mucosa during both insertion and withdrawal. The distance to the squamocolumnar junction (SCJ), the “Z-line,” where the white squamous esophageal mucosa meets the red columnar gastric epithelium, is recorded in the procedure report. The site of the diaphragmatic crura (hiatus) should also be recorded and is seen as impression into the esophageal or gastric lumen. This point can be accentuated by asking the patient to sniff while the area is visualized. The endoscope is then advanced into the gastric lumen under direct visualization. Unlike colonoscopy where there is a requirement for significant torqueing or twisting of the scope, due to fixation of the esophagus in the mediastinum, EGD manipulations can be more directly achieved with deflection of the wheels and movement of the handpiece (“dancing with the scope”).

After aspirating any gastric contents, the 4 gastric walls are surveyed using combinations of tip deflection and shaft rotation, insertion, or withdrawal. During upper endoscopy, the endoscope will naturally follow the greater curvature as it advances toward the antrum, and this is called the “long position.” This affords an end-on view of the pylorus, which is approached directly. Passage through the pylorus can usually be facilitated by gentle pressure and air insufflation. Entry into the duodenal bulb is recognized by
the typical granular, pale mucosa without the folds of the valvulae connivente. Finally, the second portion of the duodenum is entered with the associated folds, by deflecting the tip up and to the right. In addition, rotating the handpiece to the right will help facilitate this maneuver. Withdrawal of the endoscope at this point while keeping the tip deflected leads to paradoxical advancement of the endoscope down the duodenum. Withdrawal of the endoscope places the shaft along the lesser curvature of the stomach and allows for this paradoxical forward advancement of the tip. This is referred to as the “short position.” All areas should be carefully surveyed again as the endoscope is withdrawn.

The final component of a diagnostic EGD is evaluation of the cardia, fundus, and incisura along the lesser curvature. With a forward-viewing endoscope, these sites are visualized by a retroflexion maneuver with full upward tip deflection (Figs 5-4 and 5-5).

**FIGURE 5-4** Retroflex view in the stomach, here revealing a large type III paraesophageal hernia.
FIGURE 5-5  In another retroflex view, an intact surgical fundoplication is seen.

**Techniques of Endoscopic Tissue Sampling**

Sampling of tissue is most frequently obtained by passage of a spiked forceps via the endoscope’s biopsy channel. Multiple biopsies should usually be obtained. For ulcers, one should biopsy the edge of the lesion in at least 4 quadrants. Standard biopsy techniques are quite superficial; however, if deeper biopsies are desired, these can be obtained by using either a jumbo forceps or the practice of repetitive biopsies at the same site, which will lead to a deeper sampling.

Surveillance in diseases such as ulcerative colitis and Barrett esophagus requires a standardized sampling technique. Ulcerative colitis protocols recommend biopsies every 10 cm throughout the entire colon, and Barrett sampling per the Seattle protocol requires at minimum 4-quadrant biopsies every 1 cm using a jumbo forceps. The goal of these sampling techniques is to identify the presence of dysplastic tissue necessitating further intervention.
Tissue and lesions can also be sampled by the use of brush cytology. In this technique, a sleeved brush is passed through the biopsy channel of the scope and rubbed forcefully over the desired site. The brush head is extended, stirred in a fixative solution to be spun down for cell evaluation, and then transected and dropped into fixative for direct cytologic analysis. The sensitivity and specificity of this technique are dependent on direct approximation to the diseased mucosa and should not replace a directed biopsy if attainable.

**THERAPEUTIC ENDOSCOPIC INTERVENTIONS**

**Management of Bleeding**

Endoscopy plays a critical role in evaluation and treatment of UGI bleeding. The degree of rapidity of UGI bleeding varies from severe with gross hematemesis to mild, presenting as either heme-positive stools or iron deficiency anemia. The timing for EGD should be based on each individual clinical scenario, understanding that endoscopy is both a diagnostic and a therapeutic tool. In all patients, hemodynamic stabilization and correction of any sources for ongoing coagulopathy are a priority.

Endoscopic hemostatic therapies can be divided into thermal and nonthermal categories. In addition, these hemostatic options can be further delineated based on specific ideal applications. There are associated risks with each of these techniques, which must be understood to allow for appropriate tool selection. It is also possible to treat bleeding with combined modalities such as coagulation and injection or clipping and injection. When comparing individual therapeutic techniques, there is very little difference between them in terms of providing successful hemostasis. In fact, numerous studies demonstrate the superiority of combined over single hemostatic therapy. Given the relatively high success rates of controlling UGI bleeding by endoscopic modalities, it is appropriate to pursue endoscopic means whenever available before seeking surgical or interventional radiology options.19
THERMAL TECHNIQUES

Thermal therapies control hemorrhage by inducing tissue coagulation, collagen contraction, and vessel shrinkage. Thermal energy is delivered via a contact or a noncontact device. Thermal therapies are successful in 80% to 95% of cases, with a rebleed rate of 10% to 20%. These techniques are easy to use and safe, with a perforation rate of 0.5%, although this is dependent on the site of the gastrointestinal tract, with the cecum more likely to result in perforation than a thicker organ such as the stomach.\textsuperscript{20}

**Contact Thermal Techniques.** Contact or coaptive techniques involve the use of probes passed via the biopsy channel, which allow for pressure tamponade of the bleeding point with simultaneous application of thermal energy for coagulation. The firmer one applies the device to the tissue, the greater is the depth of energy penetration. In addition, the tamponade not only improves visualization but also reduces the “heat sink” effect of active bleeding, and thereby improves the efficiency of the coagulation process. Multipolar (bipolar) cautery (Fig. 5-6) and heater probe devices are used most commonly, although monopolar cautery via a biopsy forceps or snare may also be employed, albeit with a potentially higher risk of injury. The heat generated, which can reach several thousand degrees, is sufficient to cause full-thickness tissue damage, so care is required when using this modality.
Both cautery and heater probe units allow pulse irrigation to be performed for visualization and clot clearance via foot pedal control. Variables important in achieving hemostasis include probe size, force of application, power setting, and duration of energy delivery.\textsuperscript{20,21} Vessels of up to 2 mm in diameter appear to be able to be well controlled by these techniques, although the overall surface area treated by these devices is limited by the size of the probes.

**Noncontact Thermal Techniques.** Argon plasma coagulation (APC) is a technique in which thermal energy is applied to tissue via ionized argon gas. This technique has the disadvantage of not allowing a tamponade effect, but conversely is not prone to adherence of the probe to the hemostatic
coagulum. The gas has an effect of clearing luminal liquid from the point of application; however, due to the high pressure of gas delivery, one must be careful to avoid overdistention of the lumen by using frequent suctioning during APC usage. It is more widely used in most centers than laser and, in limited studies, appears to have similar efficacy to contact probes.\textsuperscript{21}

APC is particularly well-suited for settings where large mucosal areas require treatment such as gastric antral vascular ectasia (GAVE) (Fig. 5-7), or where the risk of deeper thermal injury leading to perforation is of heightened concern, for example, cecal angiodysplasia.

**FIGURE 5-7** Endoscopic image of gastric antral vascular ectasia (GAVE) representing a diffuse disease best treated with argon plasma coagulation.

**NONTHERMAL TECHNIQUES**
Injection Sclerotherapy. Injection therapy is performed by passage of a catheter system through the biopsy channel of the endoscope. There is an internal 5-mm needle that can be advanced and withdrawn as needed. The sclerosant is injected submucosally. Injection therapy at 3 or 4 sites surrounding a bleeding site prior to contact thermal techniques may prove more effective, as the created eschar is occasionally removed inadvertently affixed to the treating probe. If tamponade is provided first with injection therapy, bleeding following initial thermal therapies can be reduced. The amount injected varies with different agents, and it must be remembered that systemic absorption will occur. Dilute 1:10,000 epinephrine solution is the most commonly used agent and should be limited to less than 10 mL total volume. Other agents available include absolute alcohol, thrombin in normal saline, sodium tetradecyl sulfate, and polidocanol. For esophageal varices, injections are begun just above the GE junction. Sclerosants can be injected either directly into the varix or along side it, intravariceal or paravariceal. Variceal banding with endoscopic band ligators, although associated with a slightly higher rate of rebleeding, has predominantly supplanted injection sclerotherapy due to lower complication rates. In the absence of active bleeding or stigmata of bleeding, prophylactic endoscopic variceal eradication should not be performed because of the high risks of complications associated with the procedures. In patients with severe variceal bleeding or recurrent bleeding following endoscopic therapies, other options such as transjugular intrahepatic portosystemic shunt (TIPS) or surgical portosystemic shunting should be considered (see Chapter 46).

For gastric varices, injection with cyanoacrylate has been recently shown to be more efficacious then band ligation. Many case series report a success rate of 90% or higher in arresting bleeding in gastric varices with injection cyanoacrylate or thrombin. Although most of the data have been from Europe where histoacryl (N-butyl-2-cyanoacrylate) is used, similar success has been reported using Dermabond (2-octyl cyanoacrylate) in the United States. Cyanoacrylate therapy appears to be superior to sclerotherapy or band ligation for controlling acute gastric variceal hemorrhage and also at preventing rebleeding.

Endoscopic Ligation Techniques

Endoscopic Band Placement. Endoscopic band ligating systems are readily
available, provide an alternative for management of variceal and nonvariceal bleeding, and are routinely used in conjunction with endoscopic mucosal resection (EMR) techniques. This technique is based on the ability to suction tissue into a cap placed at the tip of the endoscope and then, with the turning of a control knob, fire a small tightly constricting rubber band. Single-band devices were initially developed for the treatment of esophageal varices, but there are now numerous multiband ligating systems. This innovation provided an alternative to injection sclerotherapy, and although it proved to be slightly less effective in preventing recurrent bleeding, complications such as stricture formation have been dramatically reduced. Applications for endoscopic banding include treatment of internal hemorrhoids, Dieulafoy ulcers, esophageal and gastric varices, and mucosal neoplasia in conjunction with EMR.\textsuperscript{24}

**Endoscopic Suture Placement.** Pretied endoscopic loops can also be applied through a standard endoscope biopsy channel and can be used for ligation of pedunculated structures before or after endoscopic resection. These single-application devices are similar to laparoscopic endoloops, although they are nylon sutures, and instead of an actual slip knot, a plastic cinching device holds the loop in place once deployed. Use of a double channel endoscope, allowing for a 2-handed technique to grasp the desired tissue and deliver it through the opened loop, is preferred. Similar to clips, these sutures will routinely slough off the tissue in 1 to 2 weeks.

An endoscopic suturing device currently in clinical use is the OverStitch (Apollo Endosurgery). Although used more often for intraluminal closure, it has been used for bleeding control as well. It is loaded onto a double-lumen scope (GIF 2T160, Olympus Corporation, Tokyo, Japan). The principle is similar to the laparoscopic Endo Stitch with a detachable needle tip that carries an absorbable or nonabsorbable suture. There is a tissue helix device that comes through the channel as well for retracting tissue closer to the device for deeper purchase by the suture. It is shown in Fig. 5-8. The sutures can be placed in a short running fashion or individual interrupted sutures without removing the device. Its use in acutely bleeding patients has been very limited due to logistical difficulties of specialized equipment and technical complexity required to use it. It has been used for control of bleeding after endoscopic resections such as EMR or endoscopic submucosal dissection (ESD).\textsuperscript{25}
Endoscopic Clipping. Endoscopic clip placement is an effective method to control bleeding and can be used safely at multiple sites throughout the gastrointestinal tract.\textsuperscript{26-28} Frequently, more than 1 clip is necessary at the site of bleeding (Fig. 5-9). The depth of tissue obtained by endoscopic clip placement is quite superficial, with only the mucosa routinely being captured. Clips are placed via the biopsy channel of the scope and come with varied application and shape qualities. Rotatable clips as well as clips that can be opened and closed prior to final positioning are available. In addition, clips with both 2 arms and 3 arms, as well as those that have single-use and multiple-use deployment systems, are manufactured. These clips can effectively control bleeding and usually fall off in 1 to 2 weeks. Cases of clips remaining at the site with and without mucosal overgrowth months after placement have been reported.
Over-the-scope clips, as the name implies, go over the scope and are similar to band ligators in initial setup. The Ovesco clip is currently available in the United States and is a nitinol-based bear claw type of clip, as shown in Figs 5-10 to 5-12.

The clips come in 3 sizes and can go on a therapeutic or diagnostic scope. Clip deployment is similar to band ligation with a string wire attached to a deployment wheel. The target lesion can be suctioned in the cap, or if it is indurated and scarred tissue, it can be engaged in a tripronged anchoring device to bring the tissue in for clipping.

Reports of its clinical efficacy have been limited to small case series, but they are encouraging, with an overall success rate of 71% to 100% for bleeding lesions. The clip has been used both as a primary modality and for rescue.

**Endoscopic Mucosal Resection**

The treatment of premalignant and superficial cancers can now be managed
by endoscopic resective techniques. EMR has been employed for adenomas, dysplastic lesions, and early-stage carcinomas, including lateral spreading tumors. Carcinomas without submucosal invasion or nodal spread might be amenable to EMR. Although these diseases are less commonly seen in Western societies, the use of these techniques is routine throughout Asian populations for treatment of esophageal and gastric lesions. Conversely, colonic lesions in Western countries are routinely managed with these modalities. Computed tomography (CT) scan and EUS are recommended to assess for nodal disease prior to EMR. Multiple technical variations of EMR for the upper and lower tract have been developed, including submucosal injection, “suck-and-cut,” “suck-and-ligate,” and strip biopsy.

**SALINE LIFT EMR**

The most commonly performed EMR technique employs submucosal injection of a fluid followed by electrosurgical polypectomy. Initially the margins of the lesion are clearly delineated, and the periphery is marked using a short burst of electrocautery. A standard sclerotherapy needle is then used to perform a submucosal injection. The most commonly used fluid is saline with or without epinephrine, although hyaluronic acid, glycerol, and dextrose have all been described. A bleb is created with the submucosal injection creating space between the line of resection and the muscularis propria of the organ, and the lesion is resected (Figs 5-13 to 5-15). Repeat injection of agent is commonly needed due to absorption as well as diffusion of the fluid. Injection beyond the lesion first allows for better imaging of the tissues. Intraliesional injection can also be used prior to resection. One caveat to this technique is that if the submucosal injection does not result in elevation, one must consider that this mass is an invasive lesion and should not be resected endoscopically. Multiple biopsies as well as EUS should be performed.
FIGURE 5-13  Sessile colon polyp prior to saline lift EMR polypectomy.
FIGURE 5-14  Sessile colon polyp following saline submucosal injection.
FIGURE 5-15  Saline lift EMR polypectomy of sessile colon polyp. Resected polyp is seen in the distance and the polypectomy site in the foreground.

“SUCK-AND-CUT” EMR
The “suck-and-cut” technique uses a specially designed cap attached to the tip of the endoscope. A submucosal injection may be created a priori, and the lesion is sucked into the cap. A snare affixed to the cap is used to encircle the lesion, which is then resected by application of electrocautery. Similar to any thermal technique, risk of perforation exists. In addition, the depth of tissue acquisition is not well controlled, and care should be taken to avoid inadvertent perforation, especially in thinner walled organs such as the cecum.

“SUCK-AND-LIGATE” EMR
The “suck-and-ligate” technique transforms a sessile or nodular lesion into an artificial pedunculated polyp, which can then be resected with standard
polypectomy techniques. A band ligating device is attached to the tip of the endoscope, and the tissue is sucked into the cap and a band is placed at the base of the lesion. This is done with or without saline lift injections prior to banding. This serves to separate the mucosal lesion from the submucosa, permitting safe resection using a standard polypectomy snare.

The most frequent complications of EMR are bleeding and perforation. Immediate bleeding can be controlled with endoscopically placed clips or injection of dilute epinephrine. Electrocautery should be used judiciously after EMR because the thin submucosa and serosa are susceptible to full-thickness injury with cautery. Delayed bleeding often requires repeat endoscopy with injection therapy or clip application, although angiography and embolization may be an alternative. Perforations can also be managed endoscopically with endoscopic clips as well as temporary enteral stent placement to cover the site of perforation.

ENDOSCOPIC SUBMUCOSAL DISSECTION

An extension of EMR that has been recently reported for endoscopic resection of more extensive lesions is ESD. Using a combination of needle cautery and blunt endoscope cap dissection, large segments of tissue can be resected. Two-handed techniques using a double-channel scope is vital. Circumferential segments of tissue can be removed, although these are lengthy and very challenging procedures. The advantage of ESD is that it represents a more classic oncologic maneuver, as compared to the piecemeal resection that occurs with other EMR techniques, in that margins as well as lesion depth can be more accurately pathologically evaluated. Complications are higher than for the other EMR techniques, including bleeding, perforation, and stricture formation, which can occur in almost 20% of cases.

ENDOSCOPIC MUCOSAL ABLATION

Endoluminal therapies for ablation of mucosal-based diseases such as Barrett esophagus have recently seen great advances. Previously, photodynamic therapy (PDT) was the principal technique used, but the associated complications and the side effects related to the delivery of the sensitizing agent were high. Endoscopic radiofrequency ablation (RFA) has largely
replaced it and gained acceptance for treatment of intestinal metaplasia as seen in Barrett esophagus. Its unique design incorporates bipolar radiofrequency energy and applies it directly to the esophageal epithelium for ablation. A balloon-based system, as well as a directed planar electrode device implementing this technology, has been used in this form of therapy. The balloon-based model has proved to be safe for Barrett’s esophagus.

The HALO system (BÂRRX Medical, Sunnyvale, CA) is an endoscopic RFA device composed of an ablation electrode that is mounted to the end of a flexible endoscope. The system comes in HALO, HALO, and HALO sizes depending on the degrees of circumference to which it needs to be applied. The HALO applies circumferential energy, and the rest are more focal. The energy is directed uniformly to a depth of around 0.5 mm. This endoscopic RFA technology also delivers a controlled amount of energy to the tissue that is predetermined prior to firing, thereby limiting unintentional transmural and potentially extraluminal injury.

Several studies have proven feasibility and safety for this novel therapy, with very few documented cases of postprocedural stricturing, as had been seen with PDT. For Barrett esophagus with low-grade dysplasia, RFA is becoming the therapy of choice to prevent progression to high-grade dysplasia or adenocarcinoma, which can be as high as 9.1% per year. Recent data show RFA to be very effective in eradication of low-grade dysplasia and even intestinal metaplasia. Most studies have reported eradication rates of >90% for low-grade dysplasia and >77% for intestinal metaplasia. A recent multicenter study, one of the largest studies yet, demonstrated the effectiveness of RFA in low-grade dysplasia by showing that the estimated cumulative risk of recurrence within 3 years was decreased in the RFA group at 2.9% versus 33% in the surveillance group. The durability of RFA has been shown to be very good as well, with studies showing >98% eradication of dysplasia at 2 years and over 80% to 90% eradication of intestinal metaplasia.

For high-grade dysplasia, endoscopic therapy involves EMR of visible or nodular lesions and RFA ablation of any residual Barrett mucosa. It is also been shown to be very effective in high-grade dysplasia. In several recent trials, eradication of dysplasia occurred in 74.4% to 100% of patients and eradication of intestinal metaplasia occurred in 41% to 100% of patients, whereas progression to cancer was seen in only 3% of patients at 12
Endoscopic Enteral Access

Endoscopic access to the gastrointestinal tract has become one of the most common endoscopic procedures now performed. What had previously required surgical intervention is routinely managed endoscopically. Gastric access (PEG), jejunal access (direct percutaneous endoscopic jejunostomy [PEJ]), or a combination of both (PEG with jejunostomy tube extension [PEG-J]) can be provided. Indications for access include supplemental feeding, decompression, fixation of structures, and access for medications. There are only a few absolute contraindications to endoscopic enteral access including esophageal obstruction and limited life expectancy. Patients with expected survival of less than 4 weeks should not undergo these procedures. Relative contraindications requiring individual patient selection include severe malnutrition, ascites, prior abdominal surgery, prior gastric resection, peritoneal dialysis, coagulopathy, and gastric malignancy.

PERCUTANEOUS ENDOSCOPIC GASTROSTOMY

PEG is now the preferred method for long-term feeding in patients who are unable to swallow or who require supplemental nutrition or chronic gastric decompression. PEG may be preferable to surgical gastrostomy since it is safe, less expensive, and less invasive. A variety of PEG techniques are available including “pull,” “push,” and “introducer.” “Pull” and “push” techniques require passage of the tube via the oropharynx, and it is proposed that infectious risks and seeding of oropharyngeal cancers might be increased as compared to the “introducer” technique, where the tube is placed percutaneously through the abdominal wall under endoscopic guidance. This theory has yet to be proven in randomized prospective trials.

Prior to any PEG procedure, a single dose of prophylactic cephalosporin (or equivalent) should be given intravenously. The patient is placed in the supine or semi-Fowler position with the head elevated and the arms held with soft restraints, after which the abdomen is prepared and draped using sterile technique. The endoscope is then passed into the stomach, which is distended with air insufflation. It is recommended to perform a brief but complete endoscopic evaluation of the esophagus, stomach, and duodenum to rule out
any coexistent disease that might require treatment or complicate the PEG procedure. The assistant then presses on the abdomen with a single finger and the impact against the anterior gastric wall should be noted. Ideally, this point should be 2 to 3 cm below the costal margin, and the maximal point of impression may be on either side of the abdominal wall or subxyphoid. Light transillumination from within the stomach to the skin surface may aid in identifying a safe landmark. Finally, it is imperative to perform a “safe tract” technique to assure that there is no intervening hollow viscus between the stomach and anterior abdominal wall. After anesthetizing the skin, a syringe with saline or local anesthetic is passed through the abdominal wall at the selected site while aspirating. As soon as air is appreciated in the syringe, the tip of the needle should be simultaneously visualized by the endoscopist in the gastric lumen. If not, an alternative site needs to be selected.

The endoscopist now passes a polypectomy snare through the endoscope channel at the selected intragastric site. A small transverse incision (approximately 7-9 mm) in the skin is created, and the assistant then inserts a 14-gauge intravenous cannula through the incision into the gastric lumen. The snare is then tightened around the cannula, and the inner stylet is removed.

“Pull” PEG. In the “pull technique,” a long looped suture is placed through the cannula, after which the snare is released. The suture is then firmly grasped with the polypectomy snare. The endoscope and the tightened snare are removed together, bringing the suture out of the patient’s mouth. The suture is secured to a well-lubricated gastrostomy tube at its tapered external end. The assistant then pulls on the suture until the attached tube exits the abdominal wall. The endoscope is then reintroduced and used to view the tube’s inner bolster (Fig. 5-16) as the stomach is loosely seated against the abdominal wall and the tube is properly positioned. This second intubation of the endoscope can be aided by grasping the PEG bumper with the snare passed through the endoscope. With withdrawal of the PEG through the mouth and out the abdominal wall, the endoscope is reintroduced into the esophagus. The snare is opened after esophageal intubation. The external bumper is placed loosely so that there is no tension at the PEG site and the endoscope is then removed.
FIGURE 5-16 Second intubation is recommended after PEG placement to confirm the position of the internal bumper and to exclude any postprocedural bleeding.

“Push” PEG. In the “push technique,” a guide wire rather than a looped suture is inserted through the cannula and pulled out the patient’s mouth. The gastrostomy tube, called a Sachs-Vine tube, has a long tapered tip, which can be pushed over the wire until it exits the abdominal wall. A second endoscopic intubation is recommended similar to the “pull” technique.

“Introducer” PEG. In the “introducer technique,” a guide wire is passed through the cannula placed into the stomach under endoscopic guidance. An introducer with a peel-away sheath is then passed over this wire, allowing removal of the wire and introducer. A Foley catheter or other similar gastrostomy tube is then placed through the sheath, its balloon is inflated, and the sheath is removed. The catheter is then secured to the abdominal wall. The placement of T-tags prior to performance of the introducer PEG can help to secure the stomach to the abdominal wall.

Laparoscopic-Assisted PEG. In patients with morbid obesity, prior surgery,
or intrathoracic gastric positioning, where safe access cannot be adequately determined by routine endoscopic techniques, simultaneous laparoscopy and endoscopy can be performed to complete the PEG safely. In this way, a long spinal needle can be passed under direct laparoscopic view from the abdominal wall into the gastric lumen and the PEG can be completed as described above.

**Interventional Radiology–Assisted PEG.** In patients with a “hostile” abdomen secondary to malignancy, multiple prior surgeries, or obesity where safe access cannot be endoscopically determined and laparoscopy would be challenging, a percutaneous intragastric pigtail catheter can be placed by interventional radiology under CT or ultrasound guidance. Using a rendezvous technique, a guide wire is advanced through the pigtail during upper endoscopy, and the PEG is completed.

**PEG with Jejunostomy Tube Extension.** In patients who fail to tolerate gastric feedings due to severe GE reflux or gastroparesis, transpyloric feeding can be provided via a jejunostomy tube passed through the existing PEG. There are no prospective randomized trials, however, showing a difference between intragastric and transpyloric feeding, in terms of incidence of aspiration pneumonia. The majority of cases of aspiration pneumonia are related to aspirated oropharyngeal secretions in a patient unable to protect his or her own airway.

PEG-J placement is achieved by passing a jejunal feeding tube through the PEG lumen (a 24-Fr PEG tube accommodates up to a 12.5-Fr J-tube; a standard 20-Fr PEG tube accommodates an 8.5-Fr J-tube). Endoscopically, the jejunal tube is guided into the duodenum under direct vision. A loop suture on the tip of the jejunostomy tube can be grasped by an endoscopic clip, and once in the distal duodenum, the clip is deployed onto the small bowel mucosa to secure the tube in place. These clips routinely fall off in 1 to 2 weeks, but this technique allows for easier removal of the endoscope from the duodenum without simultaneous inadvertent withdrawal of the J-tube at the end of the procedure. If there is no suture loop at the end of the jejunal tube extension, then one can be placed using a suture that easily forms a loop that will maintain its shape such as a polydioxanone (PDS) or prolene suture.

**DIRECT PERCUTANEOUS ENDOSCOPIC**
JEJUNOSTOMY TUBE

In patients with confirmed aspiration secondary to GE reflux of intragastric feedings, direct PEJ rather than PEG-J is of benefit. Feedings beyond the ligament of Treitz are associated with a lower incidence of GE-induced aspiration as compared to simple postpyloric feeding. Direct PEJ, however, is associated with increased procedural risks including bleeding, inadvertent viscus injury, and leakage. Performance of direct PEJ requires both endoscopic and fluoroscopic guidance. Using a pediatric colonoscope, the proximal jejunum is intubated, and the tip of the endoscope is fluoroscopically visualized. Abdominal wall depression with a hemostat is performed at this site to try to identify a loop of small bowel adjacent to the abdominal wall. Safe tract techniques are then used to access the identified bowel, and a “pull” PEJ is performed with either a 16- or 20-Fr tube. Second intubation with the endoscope to the PEJ site is mandatory to assure intraluminal positioning of the jejunostomy tube bumper. The authors only perform direct PEJs in a limited subset of patients. These include patients with a prior surgical jejunostomy tube that has been removed and who now need repeat access. The site of prior J-tube is usually adherent to the abdominal wall and decreases chance of surrounding viscus injury. Patients with prior esophagectomy with previous J-tubes are usually good candidates. We have also placed them in patients after a Roux-en-Y gastric bypass if they have an antecolic and antegastric Roux limb. In such patients, the Roux limb is anterior and usually up against the abdominal wall proximally 10 to 15 cm past the gastrojejunostomy. Since the small bowel loop at the gastrojejunostomy is fixed, the chance of the jejunal loop twisting around a narrow anchoring point such as a PEJ is less of a concern.

Foreign Body Extraction. Foreign bodies are ingested predominantly by 2 groups of patients: children (age 1-5 years) who accidentally swallow an object and adults who are obtunded or inebriated, have a psychiatric disorder, or are prisoners. Food impaction may occur in patients who have an underlying benign or malignant esophageal stricture or in patients with esophageal motility disorders. In addition, patients who are edentulous or have poor fitting dental prostheses are at risk for food impaction of poorly chewed meat boluses. Evidence of respiratory compromise or an inability to handle one’s own secretions indicates an immediate need for endoscopic
evaluation and extraction of the object.

When performing endoscopic extraction, protection of the airway is of vital importance. Endotracheal intubation is required in patients who are unable to handle their own secretions. An endoscopic overtube should be considered when there is concern for dropping pieces into the airway such as when removing sharp objects or multiple fragments. In addition, practicing with a similar foreign body prior to an attempted removal will allow for selection of the most appropriate endoscopic tool.

Coins represent the most common object swallowed by children, and if seen to be in the esophagus, they should be removed promptly due to the risk of pressure necrosis and fistula formation. The coin is localized and grasped with a polypectomy snare, net, or rat-tooth or tenaculum forceps. A Foley catheter is not recommended since it does not control the object well during removal and the object could become dislodged into the airway.

In the adult population, meat impaction represents the most common foreign body and should be removed if it remains for longer than 12 hours due to the risk of pressure necrosis. Gentle scope advancement at the level of the obstruction can often assist in passage of the food bolus. Piecemeal removal with baskets, nets, and snares may be needed, with care being taken to avoid passage of the foreign body into the airway. If the bolus should pass, EGD is still indicated to rule out an associated esophageal lesion.

Use of an overtube or protective endoscopic hood may greatly facilitate removal of sharp objects such as toothpicks, fish or chicken bones, needles, and razor blades. When removing sharp objects, it is important to follow the tenet of always having the sharp end trailing. If necessary, sharp objects can be carefully pushed into the stomach, rotated, and then brought out with the pointed end trailing.

Ingested button batteries must be removed immediately to prevent viscus injury secondary to a corrosive burn. These batteries usually pass readily in other parts of the gastrointestinal tract without causing harm, although all mucosal surfaces must be examined endoscopically to identify any resultant injury.

When encountered, cocaine-filled packets should never be removed endoscopically because of the risk of breakage. Close observation and expectant management is more appropriate, with expedient surgical intervention for any signs of bag rupture or bowel obstruction.
Following any foreign body removal, the endoscopist must exclude any associated underlying disease such as stricture, neoplasm, or motility disorder (Fig. 5-17). In addition, one must be aware of the possibility of delayed viscus injury secondary to pressure necrosis resulting in partial- or full-thickness injury. Emergent contrast study or CT should be used as needed to evaluate for these complications. Repeat endoscopy, motility study, or elective contrast studies may also be required based on patient’s history or continued symptoms.

**FIGURE 5-17** Classic eosinophilic esophagitis seen in a patient with history of dysphagia and prior food bolus. Endoscopic biopsies with identification of increased eosinophils confirms the diagnosis.

Other nonobstructing foreign bodies may be identified in postsurgical patients. Intraluminal suture migration may lead to symptoms of pain or dysphagia. (Fig. 5-18). Removal with endoscopic scissors may relieve the patient’s symptoms of pain or dysphagia.
FIGURE 5-18 Sutures can be seen at the site of a prior gastrojejunostomy.

**Endoscopic Dilation.** Endoscopic dilation can be performed for any enteral stricture that can be accessed by endoscopic means. The endoscopic component of dilation may include identification, passage of a guide wire, or delivery of a dilating balloon via the endoscope channel. Strictures secondary to ischemia, inflammation, radiation, neoplasm, and postsurgery are all amenable to endoscopic dilation. The use of fluoroscopy as an adjunct to endoscopic dilation is believed to decrease the risk of perforation, although this has not been fully proven in randomized prospective trials. In addition, the type of sedation used depends on the clinical status of each individual patient, as those with tight esophageal strictures may be best served with elective airway protection.

Although several types of dilators have been used, the 2 most common
dilators used are the guide wire–driven type, which applies both axial and radial forces, and the balloon type, which applies only radial forces. Treatment is safer when performed by incremental dilations over successive sessions. A general approach is to limit the number of dilations to 3 successive balloon or dilator sizes in 1 session. Injection of steroid solutions (Kenalog) into the stricture may reduce the severity of postdilation inflammation, scarring, and restricture. The frequency of dilation will depend on the severity of the stricture and the patient’s symptoms.

Balloon dilators are used for short strictures, stenotic stomas, and achalasia. These dilators can be passed over a previously placed guide wire and are delivered through the endoscope’s therapeutic channel. Fluoroscopic guidance for balloon dilation allows the endoscopist to gauge several components of the procedure. First, it assures the positioning of the balloon in the viscus lumen. Second, if contrast is injected in the balloon as the dilating fluid, expansion of the balloon fully can be appreciated. This is termed “waist ablation” and refers to the full dilation of the balloon at the site of the stricture. The balloon changes from an hour glass appearance to a full elliptical-shaped figure.

Long, complex strictures may be less responsive to endoscopic dilation and may also require repeat treatments. Aggressive biopsying of the mucosa after dilation is necessary in cases of unclear etiology. Complications secondary to endoscopic dilation include bleeding, perforation, mucosal tears, and recurrent structuring.

Commonly encountered strictures also include post–bariatric surgery strictures. They can occur after a Roux-en-Y gastric bypass or, less commonly, after a sleeve gastrectomy. The stricture rate after a Roux-en-Y gastric bypass can be 4% to 6%. Early strictures (<90 days postoperatively) respond very well to balloon dilation, with over with over 90% responding to endoscopic intervention. Late strictures have a much higher failure rate and often require surgery. If the scope cannot get through the anastomosis, then it is best to use a wire-guided balloon with fluoroscopic guidance. The internal diameter of even a 25-mm circular stapler is only around 16 mm, so dilation is typically done until 12 to 15 mm if the starting diameter was not very small. Otherwise, a graded approach with initial dilation to 10 mm and then repeating the scope in 1 to 2 weeks and dilating to 15 mm should be done. The overall perforation rate is approximately 2% to 3%, so caution is warranted while
Sleeve stenosis is slightly less common and can occur in 1% to 3% of patients. Due to the high volume of sleeves being done currently, sleeve stenosis is going to be encountered more often. These can be harder to treat and do not respond well to standard controlled radial expansion balloon dilations. Endoscopic success rates are higher with dilation using 30-mm achalasia balloons.

**Enteral Stent Placement.** Over the past several years, endoscopic stent technology has made impressive strides in providing tools for increasingly complex clinical scenarios. Both the delivery systems and the stents themselves have gone through significant changes and allowances for treatment of a multitude of benign and malignant disease processes. Strictures, leaks, fistulae, and obstructing neoplasms have all been approached with enteral stents.

**Stent Delivery Systems.** Based on the location of the gastrointestinal tract that is to be treated, as well as the characteristics of the stent desired, endoscopic stent deployment is either through-the-scope (TTS) or wire guided. TTS stents are delivered through the endoscope channel and are routinely a 10-Fr system and require a therapeutic scope. Only uncovered self-expanding metal stents (SEMS) have a TTS characteristic. The remainder of stents all use wire-guided systems and are placed under fluoroscopic guidance. Stent delivery systems are further categorized as proximal or distal deploying based on which end of the stent is opened first. In patients undergoing stent placement in the proximal esophagus, proximal deploying stents are preferred. Otherwise, most stent systems use a distal deployment pattern. Non-TTS stents are limited to the esophagus including the esophagogastric junction. In patients following gastric resection, these systems can also traverse a gastrojejunal anastomosis. TTS systems, conversely, can reach any site in the gastrointestinal tract that can be accessed by a therapeutic endoscope.

**Stent Characteristics.** Covered endoscopic stents have been created for the sole purpose of temporarily bridging esophageal and proximal anastomotic leaks and fistulae. The fully covered nature of the stent impedes tissue ingrowth as would occur with an uncovered enteral stent, and thereby allows
removal after 2 to 3 months once the fistula has been cured. With the increased frequency of bariatric procedures, anastomotic complications secondary to Roux-en-Y bypass are routinely managed with placement of endoscopic stents.

Removable stents are subdivided into plastic or hybrid based on the underlying structural platform. As stated earlier, fully covered silicone stents, which are self-expandable but require the use of a large deployment system, can reach as far as the proximal stomach. Similarly, covered SEMS (hybrid) stents are also placed outside of the endoscope under fluoroscopic guidance and can reach the proximal stomach as well. The greatest problem with these stents is the high risk of migration. If placed across a gastrojejunostomy, this can result in small bowel impaction of a migrated stent, resulting in the need for surgical extirpation. Bleeding, perforation, and obstruction are far less common complications. Stent migration has been shown to be significantly reduced in several recent publications with the use of the Apollo OverStitch endoscopic suturing device described earlier in the chapter. It has been reported to decrease migration rates of 30% to 60% down to around 10%. Some fully covered stents such as the EndoMAXX (Merit Medical) have antimigration struts to decrease migration rates, but data are still pending on their efficacy. Outside the United States, larger stents, such as the MEGA stent (TaeWoong Medical, South Korea), have been developed that are longer and with a larger diameter, which can be useful to treat leaks such as sleeve gastrectomy leak with possibly less migration.

Uncovered enteral stents, using TTS deployment systems, are not intended for removal and can be placed for temporary relief of benign and malignant strictures throughout the gastrointestinal tract. They are associated with increased tissue ingrowth and occlusion as compared to covered stents but have a lower rate of migration. In unresectable disease states, palliation of obstruction with enteral stents can provide an alternative to surgical bypass procedures. In addition, endoscopic stent placement in patients with obstructing colon lesions can allow for immediate decompression followed by semielective resection and primary anastomosis, rather than an initial diverting stoma.

**Endoluminal Treatment of GERD**
Numerous endoluminal treatments for GERD have been introduced over the past 10 to 15 years and have had varied clinical success. These technologies were based on suturing, tissue bolstering, or energy delivery. Unfortunately, due to many factors including marginal patient improvement, limited physician acceptance, severe complications, and corporate financial difficulties, most of these treatments are not presently available in the United States. Examples of each of these modalities include the EndoCinch plication device, the NDO endoscopic plication system, the Gatekeeper reflux repair system, and Enteryx polymer injections. Two endoscopic options that are being used clinically in the United States are the Stretta procedure and transoral incisionless fundoplication (TIF) using the EsophyX device.

STRETTA

Recent technologic advances have made the next advent in minimally invasive surgery, natural orifice surgery, a reality. Two such advances that are changing foregut surgery are the Stretta and EsophyX procedures. The Stretta (Curon Medical, Sunnyvale, CA) procedure is an endoluminal electrosurgical system that uses thermocouple-controlled radiofrequency energy delivered to smooth muscle in the area around the lower esophageal sphincter (LES) complex via an endoscopic balloon-tipped catheter (Figs 5-19 and 5-20). Introduced originally in an open-label study in 2000 to 2001, Stretta is one of the more widely studied minimally invasive treatment modalities for GERD available. It represents an alternative for patients who are either intolerant to or have an incomplete response to proton pump inhibitor (PPI) therapy or other antisecretory drugs and prefer an alternative to invasive surgery or an anatomic implant. One advantage of this technique is that it has been proven safe and effective for use even in patients who have undergone prior bariatric surgery, including fundoplication, providing an alternative to surgical revision or lifelong PPI therapy but not precluding a patient from future surgical treatment if desired. As Yeh and Triadafilopoulos describe, exclusion criteria for Stretta include the following: hiatal hernia ≥2 cm, active grade III to IV esophagitis, Barrett esophagus (metaplasia or dysplasia), and collagen vascular disease. Delayed gastric emptying is commonly found in patients suffering from GERD, but its existence does not preclude eligibility for performing Stretta. Clinically significant gastroparesis is a rarely reported and typically transient
complication of Stretta, and in fact, the procedure has been shown to normalize gastric emptying in certain patients.\textsuperscript{66,67}

**FIGURE 5-19** Patient selection criteria for the Stretta procedure. (Reproduced with permission from ©2018 Restech | Mederi-RF, LLC, Houston, TX).

**FIGURE 5-20** The Stretta procedure. (A) Normal naïve appearance of the gastroesophageal junction. (B) Positioning of balloon-basket assembly catheter at the squamocolumnar junction (SCJ). (C-E) Inflation of balloon
causing radial contact of radiofrequency (RF) electrode delivery sheaths with tissue and subsequent delivery of RF energy ablation circumferentially above and below SCJ and onto gastric cardia. (F) Resultant tissue effect of ablation causes enhanced lower esophageal sphincter (LES) muscle mass and pressure, collagen production/contraction, and increased tensile strength with decreased LES compliance, thus decreasing reflux episodes. (Reproduced with permission from ©2018 Restech | Mederi-RF, LLC, Houston, TX.)

The delivery catheter is introduced over a guide wire within a soft, 6-mm shaft as a “balloon-basket assembly” with a maximum inflation diameter of 3 cm and 4 radial electrode delivery sheaths, along with a specialized suction irrigation system. After identifying the SCJ endoscopically, the proximal end of the balloon is placed 1.0 cm above the SCJ where it is then inflated, allowing each of the 5.5-mm curved needle electrodes to enter the surrounding tissue. Radiofrequency energy is delivered over a 90-second period with ongoing tissue temperature monitoring before the balloon is deflated and its associated needle electrodes retract. The catheter is rotated 45 degrees before applying the next series of thermal injuries in similar fashion. Typically this process is repeated approximately 14 to 20 times, extending anatomically from approximately 0.5 cm above to 1.5 cm below the SCJ, followed by additional firings to the gastric cardia. The entire procedure can be done under conscious sedation in about 60 minutes. The primary aim of this technique is to decrease LES compliance and limit its transient, untimely relaxations that cause symptoms of GERD. The heat generated induces collagen production and subsequent contraction, effectively increasing LES muscle mass while shrinking other tissues, causing improved tensile strength and limited sphincter compliance.

Several early retrospective studies and randomized controlled trials examined the effectiveness of the Stretta procedure up to 12 months after treatment and demonstrated efficacy as measured by a variety of factors, including PPI requirement, GERD health-related quality of life (HRQL) scores, overall patient satisfaction, and endoscopic factors such as esophageal acid exposure, gastritis scoring, and LES pressure. Recent long-term efficacy studies confirm the durability of this endoscopic procedure. Three separate studies evaluated patients 48 months after Stretta treatment, and all revealed persistent, significant improvement in patient satisfaction and HRQL scores, and the majority of patients (78%-86.4%) were still off of PPI
therapy. This is comparable if not superior to reported rates of long-term antacid use after fundoplication (23% PPI use and 41% all antacid use), although this may be deceiving because many patients who take antacids after fundoplication do not have objective evidence of ongoing reflux.

A systematic review and meta-analysis published in 2017 showed some mixed results. Twenty-eight studies (4 randomized controlled trials, 23 cohort studies, and 1 registry) with a total of 2468 patients were analyzed. Pooled results showed that although Stretta improved HRQL and standardized heartburn scores, 49% of the patients still required PPIs at follow-up. Endoscopic therapies such as Stretta may represent a growing paradigm shift in the armamentarium of antireflux therapy from traditional invasive surgical procedures. It may also be helpful as a procedure in rescue therapy after other surgical procedures, such as for recurrent symptoms after fundoplication, as well as after certain bariatric procedures. Reflux is increasingly common after a sleeve gastrectomy, and currently, there is a multicenter trial that is under way to investigate its efficacy in such patients.

**ESOPHYX**

The EsophyX system (Endogastric Solutions) represents an alternative to classic laparoscopic antireflux surgery via endoluminal fundoplication, or TIF. This device attempts to create a nipple valve similar to that created with fundoplication via a series of serosa-to-serosa plications, that effectively wrap the stomach fundus around the cardia. This TIF procedure has evolved clinically over time from a first generation TIF 1.0 gastro-gastric plication at the Z line, to the subsequent TIF 2.0 that creates a longer 3-4cm valve beginning above the Z line and a superior rotational element of 270-310 degree esophago-gastric plication. It is a disposable device that is placed axially atop a standard endoscope introduced orally and advanced to the level of the Z line and beyond. Two separate physicians are typically required to perform the operation—one to control the endoscope and one to control the device. As Testoni and Vailati describe, the EsophyX instrument consists of “a handle with controls, a 18-mm diameter chassis through which control channels run and a standard front view 9-mm diameter endoscope can be inserted; the tissue invaginator, constituted of side holes located on the distal part of the chassis, to which external suction can be applied; the tissue mold, which can be brought into retroflection and pushes tissue against the shaft of
the device; a helical screw, which is advanced into the tissue and permits to retract the tissue between the tissue mold and the shaft; two stylets, which penetrate through the plicated tissue and the tissue mold, over them polypropylene H-shaped fasteners can be deployed; a cartridge containing 20 fasteners” (Figs 5-21 and 5-22). With the anesthetized patient in the left lateral decubitus position, the endoscope and device are advanced to the level of the stomach under direct visualization. Along with significant bleeding, esophageal perforation has been identified as a potential serious complication, and extra care should be exercised during insertion of the device-endoscope combination. The esophageal invaginator component engages the esophagus at or above the Z line and reduces a (small) hiatal hernia if present with distal device advancement. To effectively reconstruct the GE junction, an omega-shaped valve similar to surgical fundoplication is created by grasping gastric fundal tissue between the main body and tissue mold of the device beginning posteriorly at the greater curve and firing a series of full-thickness polypropylene fasteners across the grasped tissues, forming an abutted serosa-serosa tissue flap. The procedure proceeds anteriorly until a 2- to 6-cm flap and 200- to 310-degree (normally 270 degrees) fundoplication is created. The EsophyX device is removed and the repair investigated for quality with the remaining endoscope. The entire procedure takes about 1 hour, with an average of 14 fasteners fired.
FIGURE 5-21  Schematic representation of the EsophyX procedure. Step 1: The EsophyX device enters the esophagus through the mouth and is positioned at the gastroesophageal junction (GEJ) to rebuild the valve. Step 2: A full thickness tissue fold at the GEJ is retracted, wrapped and secured using SerosaFuse® implantable fasteners—equivalent to 3-0 sutures—to create an esophagogastric plication. Step 3: The valve is extended and approximately 20 fasteners are delivered to form at 270° wrap. The TIF® 2.0 procedure reconstructs the primary components of the antireflux barrier, creating a tight 3cm length valve enveloping the distal esophagus below the diaphragm.

The EsophyX® Device, with the flexible endoscope placed down the center channel of the device, is introduced through the mouth into the esophagus as one unit. The endoscope is retroflexed and device is positioned at the gastroesophageal junction (GEJ) to rebuild the valve.

The EsophyX procedure forms a valve to prevent reflux.
All patients should have preoperative endoscopy and esophageal manometry performed, because increased failure rates are witnessed in patients with esophageal dysmotility and hiatal hernias >2.0 cm in length.\textsuperscript{84,86} In addition, cases of severe preoperative PPI-refractory disease seem less likely to be successfully treated by EsophyX, and standard surgical repair shows trends of superior long-term, symptom-free recovery.\textsuperscript{84,87} Meanwhile, the number of fasteners used is predictive of success, with more fasteners (14-20) connected with decreased failure rates.\textsuperscript{86} Although some discrepancy existed among early studies examining the short-term efficacy of EsophyX, a recent systematic review showed an overall patient satisfaction rate of 72%, overall rate of PPI discontinuation of 67%, a 7.2% failure rate, and a 3.2% incidence of major complications at a mean follow-up of 8 months.\textsuperscript{86} Other studies evaluating long-term outcomes as long as 3 years postoperatively have shown sustained improvement in GERD HRQL scores but lower rates of persistent PPI discontinuation of approximately 40% (42%-71%); 70% to 75% of patients were either off PPI or their dose was halved, with
approximately 25% (21%-31%) of patients requiring the same dose as preoperatively.\textsuperscript{84,86,88,89} Reintervention with laparoscopic fundoplication for patients with TIF failure has demonstrated efficacy but is associated with higher complication rates such as GE perforation and abscess formation.\textsuperscript{90,91}

Outcomes at 3 and 5 years have been recently reported from a prospective, randomized controlled trial called TEMPO (TIF EsophyX vs. Medical PPI Open Label). This was an open-label TIF versus PPI trial with cross over at 6 months of the PPI patients to TIF. Primary outcomes evaluated troublesome regurgitation and atypical symptoms at 3 and 5 years postoperatively, while secondary outcomes evaluated included symptom scores such as GERD-HRQL, PPI use, reoperation, and patient health outcomes satisfaction. TIF 2.0 performed quite well, with elimination of troublesome regurgitation in 90% of patients at 3 years, and 86% at 5 years, atypical symptom relief in 88% at 3 years and 80% at 5 years, and 66% of patients were off of PPI therapy (insert prior reference #92 here along with the new reference listed below). Three patients (5%) underwent reoperation, opting for fundoplication. A decrease in the total GERD-HRQL score was seen from 22.2 to 6.8 at 5 years (P < .001).\textsuperscript{92} A total of 5 randomized controlled trials using TIF were published between 2014 and 2015.\textsuperscript{93} A subsequent systematic review and meta-analysis that included 13 prospective observational studies showed reduction in total number of reflux episodes and reduction in acid exposure compared to sham without PPI.\textsuperscript{93} PPI usage is shown in Fig. 5-23.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure523.png}
\caption{Long-term outcomes of PPI use after TIF in prospective}
\end{figure}
Although most patients had reduction in PPI usage, cessation of PPIs showed a reduction over time and peaked at approximately 70% at 6 months but decreased to 40% or below for the limited number of patients who had a 5- and 6-year follow-up. Some of the longest outcomes available are for TIF 1.0, which was used in 5 of the 18 studies in this review, whereas 13 studies used the TIF 2.0 with the esophagogastric plication. Taken together, these data appear to support TIF 2.0 with EsophyX as a relatively safe and efficacious procedural alternative to invasive fundoplication, but such outcomes will need to be followed over time.

Endoluminal Bariatric Therapies

The field of endoluminal bariatics has been rapidly expanding lately. There is increasing recognition that some weight loss interventions need to be available that may have lower efficacy than surgery but have lower costs and lower risk. The spectrum of intervention is shown in Fig. 5-24. Endoscopic bariatric therapies may be less invasive, cheaper, reversible, and repeatable. They may serve as a primary therapy, as a bridge to bariatric or other surgeries, or as a rescue or revisional procedure for prior bariatric surgery. They can consist of restrictive, metabolic, and aspiration therapy.
FIGURE 5-24 Therapeutic approach to obesity treatment. The effect of endoscopic bariatric treatment for weight loss is greater than that of drugs but lower than that of bariatric surgery, but endoscopic bariatric treatment features fewer complications than bariatric surgery. BPD, biliopancreatic diversion; DS, duodenal switch; RYGB, Roux-en-Y gastric bypass; VBG, vertical band gastroplasty. (Reproduced with permission from Choi SH, Chun HJ. Recent trends in endoscopic bariatric therapies, Clin Endosc 2017 Jan;50(1):11-16.)

INTRAGASTRIC BALLOONS

Three US Food and Drug Administration (FDA)–approved gastric balloons are now available in the United States. These include the Orbera (Apollo Endosurgery), Reshape Duo (Reshape Medical), and Obalon (Obalon Therapeutics). These can be inserted with a catheter-based delivery system that is place side by side along the endoscope, as in the Orbera or Reshape balloons, shown in Fig. 5-25. The Obalon balloon is initially swallowed in an absorbable capsule that is attached to a microcatheter that is then used to inflate balloon. Retrieval for all the balloons is endoscopic and usually at 6 months, at least in the United States where they are approved to be left in for 6 months.  

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**FIGURE 5-25** The three different balloon types on the market. (Reproduced with permission from ASGE Bariatric Endoscopy Task Force; ASGE Technology Committee, Abu Dayyeh BK, et al: Endoscopic bariatric therapies, Gastrointest Endosc 2015 May;81(5):1073-1086.)

**GASTROINTESTINAL ENDOSCOPY**

The Orbera, previously known as the Bioenterics balloon, has had the largest worldwide experience. Although it has been modified over the years, it has been used in Europe and elsewhere for over 20 years. The weight loss results from these balloons are modest compared to bariatric surgery but are acceptable and are around 25% of excess weight.\(^{94,95}\)

**ENDOSCOPIC SLEEVE GASTROPLASTY**
This is an endoscopic gastric volume reduction most commonly performed now with the Apollo OverStitch device described earlier, although other devices have been used as well (Fig. 5-26). Results are mainly from small case series and are better than intragastric balloons, with excess weight loss in the 30% to 40% range. Because these are supposed to be full-thickness sutures, a few complications, such as abscess and bleeding from splenic injury, have been reported but are rare.

**FIGURE 5-26** An illustration of the suturing sequence for the creation of the endoscopic sleeve gastroplasty. (Reproduced with permission from Abu Dayyeh BK, Rajan E, Gostout CJ: Endoscopic sleeve gastroplasty: a potential endoscopic alternative to surgical sleeve gastrectomy for treatment of obesity, *Gastrointest Endosc* 2013 Sep;78(3):530-535.)

**ASPIRATION THERAPY**

Recently the FDA approved a gastrostomy tube–type device that is a PEG-like silicone tube. It was approved for patients with a body mass index of 35 to 55 kg/m² and removes about 30% of ingested food approximately 30 minutes after eating by attaching a small portable suction pump to the tube, as shown in Fig. 5-27. Early weight loss results have been impressive and better than intragastric balloons.

SMALL BOWEL ENDOSCOPIC BARIATRIC THERAPIES

None of these therapies have been FDA approved as of early 2017, but they are actively being studied (Fig. 5-28). Small bowel endoscopic bariatric therapies include the duodenojejunal (EndoBarrier; GI Dynamics) and the gastroduodenojejunal bypass liners (ValenTx).
The EndoBarrier duodenojejunal liner is a 65-cm plastic liner anchored in the duodenal bulb with a nitinol crown like a stent (Fig. 5-29). It is placed with endoscopic and fluoroscopic guidance with a catheter delivery system beside the scope. Excess weight loss was approximately 25%, and a pivotal multicenter randomized controlled trial was under way in the United States but was stopped before completion due to higher than expected hepatic abscess rate. There have been favorable results from of metabolic effects on hemoglobin A1c. The ValenTx gastroduodenojejunal liner is anchored in the distal esophagus and is 120 cm long. There are ongoing efficacy studies under way.
Intestinal bypass procedures are being performed with endoscopic placement of self-assembling magnets that eventually erode through and pass and leave a viable anastomosis to be formed. Endoscopic metabolic therapy is also being administered through a procedure known as duodenal mucosal resurfacing or remodeling. In this endoscopic procedure, a thermal ablation is done of the superficial duodenal mucosa with hot water through a catheter after a saline lift of the mucosa. Its effects may be mostly metabolic with beneficial effects on glucose metabolism.

**ENDOSCOPIC INTRAMURAL SURGERY**

There currently are 2 natural orifice transluminal endoscopic surgery procedures that are increasingly being adopted. These are per-oral endoscopic myotomy (POEM) and per-oral pyloromyotomy (POP; also known as G-POEM). Up until the past few years, management of achalasia consisted of botulinum toxin injection, pneumatic balloon dilation, and surgical intervention with Heller myotomy. Dr. Haruhiro Inoue from Japan helped
develop POEM and bring it into widespread clinical use (Fig. 5-30).\textsuperscript{100,101} Although initially it was reserved for patients without sigmoid-type achalasia, it is now applicable to all patients with achalasia as a primary procedure or as a rescue after failed prior therapies, including failure after Heller myotomy.\textsuperscript{100,101}

\textbf{FIGURE 5-30} Steps in per-oral endoscopic myotomy. \textbf{(A)} Entry to the submucosal space is made after submucosal injection with saline. \textbf{(B)} The submucosa is progressively dissected distally along the muscular layer, using spray coagulation at 50 W (ERBE VIO300D), creating a submucosal tunnel extending beyond the gastroesophageal junction. \textbf{(C)} Myotomy of the circular esophageal and gastric muscle bundles is performed under direct vision. \textbf{(D)} After myotomy has been successfully completed, the mucosal entry site is closed with hemostatic clips from the distal to the proximal end of the mucosal fenestration. (Reproduced with permission from Inoue H, Sato H, Ikeda H, et al: Per-Oral Endoscopic Myotomy: A Series of 500 Patients, \textit{J Am Coll Surg.} 2015 Aug;221(2):256-264.)

The patients are prepared by having them on a liquid diet for 1 to 2 days prior to the planned procedure. If significant food retention is suspected, then an endoscopy 1 to 2 days prior is done to help clear it. Patients then remain on a liquid diet until the POEM. To reduce aspiration, endoscopic suction can be performed prior to general anesthesia but is not always done.
The procedure is done under general anesthesia. A forward-viewing endoscope is used with a transparent oblique distal cap attachment. Carbon dioxide is used for insufflation. The flow is set to a lower flow rate of approximately 1.2 L/min. First, a submucosal tunnel is created. This is started by a submucosal saline injection with indigo carmine or methylene blue around 14 cm proximal to the GE junction. A 2-cm longitudinal mucosal incision is then made and entry into the submucosal space obtained. A triangle tip knife is used for cutting. A long submucosal tunnel is then created similar to ESD, using the cap for retraction and the triangle tip knife for tissue division. It is extended to around 3 cm beyond the GE junction onto the stomach. Division of the circular muscle is then started 3 cm distal to the mucosal entry. This division of the circular muscle is continued distally until approximately 2 cm past the GE junction. The mucosal entry site is then closed with regular clips.

Worldwide experience has been rapidly increasing with POEM. Inoue et al\textsuperscript{100} have published their initial experience with 500 patients with achalasia and reported both short-term and long-term results (1- and 3-year follow-up). Table 5-4 summarizes the results, with median Eckardt score improving from 6 to 1 at 2 month and remaining at 1 at 1 to 2 years and even at 3 years for the few patients who had 3-year follow-up. In addition, the LES pressure was reduced from a median of 25.4 to 11.9 mm Hg at 1 to 2 years. GERD symptoms were present in 16.8% to 21.3% of patients.\textsuperscript{100}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before POEM</th>
<th>2 mo After POEM</th>
<th>1–2 y After POEM</th>
<th>3 y After POEM</th>
<th>P Value for Change at 3 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckardt score, median (range)</td>
<td>6 (5–8)</td>
<td>1 (0–2)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LES pressure, mm Hg, median (range)</td>
<td>25.4 (18.2–35.3)</td>
<td>13.4 (10.5–16.4)</td>
<td>11.9 (7.0–15.9)</td>
<td>11.7 (9.6–14.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endoscopic reflex esophagitis findings, n</td>
<td>LA-A, 140; LA-B, 107; LA-C, 20; LA-D, 1 (follow-up data from 414 patients, 64.7%)</td>
<td>LA-A, 68; LA-B, 25; LA-C, 15; LA-D, 5 (follow-up data from 191 patients, 59.2%)</td>
<td>LA-A, 7; LA-B, 1; LA-C, 1 (follow-up data from 16 patients, 56.3%)</td>
<td>LA-A, 8; LA-B, 1; LA-C, 1 (follow-up data from 423, 16.8%)</td>
<td>LA-A, 4; LA-B, 2.1; LA-C, 1 (follow-up data from 289, 19.4%)</td>
</tr>
<tr>
<td>GERD symptoms</td>
<td>71 (follow-up data from 423, 16.8%)</td>
<td>56 (follow-up data from 289, 19.4%)</td>
<td>13 (follow-up data from 61, 21.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription of proton pump inhibitor, n (%)</td>
<td>17 (4.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

POP, or G-POEM, is also an emerging treatment option for refractory gastroparesis. It is done along similar principles as POEM. A long overtube is usually used, but as more experience is being obtained, it is being done without one as well. A mucosal incision is made around 5 or 6 cm from the pylorus. A submucosal tunnel is created, and a pyloromyotomy is done as described earlier for POEM. The mucosal incision is then closed with clips. Early results have been encouraging. Gonzalez et al.\textsuperscript{102} reported on a series of 12 patients who underwent POP. Their gastroparesis cardinal symptoms index score improved from $3.5 \pm .8$ to $0.9 \pm 0.9$ (1 month) and $1.1 \pm 1.5$ (3 months) ($P < .001$). Gastric emptying studies normalized in 75% of patients, and 85% of the patients felt significantly better. Technical success was 100%, and no adverse events were reported.\textsuperscript{102} Several other authors have reported similar success rates.\textsuperscript{103,104}

**ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY**

**History**

William McKune, a surgeon, along with Paul Shorb, a gastroenterologist, were the first physicians to perform ERCP. In 1968, they reported on 4 cases of endoscopic identification and catheter placement into the ampulla of Vater. For the first time, imaging of the pancreatic ductal system could be seen and used for diagnostic purposes. Several years later in the mid-1970s, German and Japanese physicians described their experience in endoscopic sphincterotomy, the first therapeutic extension of ERCP. Other endoscopic adjuncts, including stone lithotriptors, plastic and expandable metal stents, and intraductal imaging tools, have fully changed ERCP from a diagnostic tool into one that is predominantly therapeutic.

**Indications**

There are numerous indications for ERCP, as listed in Table 5-5. ERCP, however, is preferentially used as a therapeutic tool due to the high risk of serious complications.\textsuperscript{105} In patients in whom a diagnostic imaging of the
pancreaticobiliary tree is desired, magnetic resonance cholangiopancreatography (MRCP) should be used. Prior to cholecystectomy for symptomatic cholelithiasis, the presence of persistent jaundice or cholangitis is the indication for preoperative ERCP. Finally, as the number of patients undergoing bariatric procedures (Roux-en-Y gastric bypass) increases, access to the ampulla has become more challenging. Identification and access to the remnant stomach routinely require surgical or radiologic intervention for performance of ERCP.

**TABLE 5-5: INDICATIONS FOR ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY**

1. Suspected choledocholithiasis
2. Identification and management of malignant or benign strictures
3. Investigation of abnormal radiographic imaging of the biliary tree
4. Persistent jaundice
5. Evaluation and treatment of sphincter of Oddi dysfunction (SOD)
6. Evaluation and treatment of pancreatic or biliary ductal injury/trauma or leaks
7. Treatment for identified ampullary adenoma
8. Recurrent or idiopathic pancreatitis
9. Treatment of complications of chronic pancreatitis including stones and/or strictures
10. Treatment for pancreatic fluid/cyst or pancreatic necrosis
11. Cytology of suspected pancreatic cancer and other pancreatic malignancies

**Patient Preparation**

Patient preparation, sedation, and monitoring for ERCP are similar to those for other upper endoscopic procedures, although the patient is routinely placed in the prone position. Patients may require general anesthesia for airway protection, as a result of inability to tolerate conscious sedation, for expected lengthy or more complicated ERCP interventions, or in the presence of multiple comorbid diseases. ERCP can be performed in a supine position, although this can make the procedure more challenging, as in patients
undergoing ERCP at the time of laparoscopic cholecystectomy.

Techniques of ERCP

ERCP is performed using a side-viewing scope and requires both endoscopic and fluoroscopic skills for interpretation and intervention. As stated earlier, ERCP is predominantly a therapeutic technique. The scope is initially passed into the esophagus blindly to a position beyond the upper esophageal sphincter and then rapidly advanced into the proximal stomach where any residual secretions should be aspirated. Unlike a forward-viewing endoscope, the pylorus cannot be visualized during intubation with a side-viewing scope. Upward deflection of the side-viewing endoscope with continued advancement will allow easy passage into the duodenal bulb.

To manipulate around the superior duodenal angle, the endoscope is turned to the right, and the tip is deflected upward to reach the second portion of the duodenum. The endoscope is then withdrawn during this maneuver, leaving the scope in the ideal “short-scope” position.

With the “short-scope” position, the endoscopist views the papilla directly along the medial duodenal wall. Very minute movements of the tip and further withdrawal of the scope will bring the papilla into view. Fluoroscopy can also be used to determine appropriate scope position and to help identify the site of the major papilla. After the papilla is visualized, it is then cannulated using one of the various types of catheters available. As the majority of ERCP cases are potentially of a therapeutic nature, most endoscopists will start with a pull wire sphincterotome. Guide wire–assisted cannulation has also become a popular practice for several reasons. First, it may minimize the overall volume of contrast required, thereby hopefully decreasing the rates of pancreatitis and cholangitis. Second, it may increase the efficiency of selectively cannulating the desired duct. Finally, it can help maintain access into the duct during catheter exchanges.

Selective cannulation of the biliary and pancreatic ducts depends on the angle of the catheter and the position of the scope tip. The pancreatic duct tends to enter the papilla in a relatively perpendicular fashion at the 1 o’clock position. In contrast, the bile duct runs toward 11 o’clock below the “lip” of the papilla.

ERCP represents an endoscopic and radiographic intervention, and proper
radiologic technique is critical to obtaining interpretable radiographs. Artifacts such as air bubbles, streaming and layering of contrast, and contrast spillage into the duodenum should be recognized and avoided.

**ERCP Therapeutic Interventions**

**SPHINCTEROTOMY**

There are 2 types of sphincterotomy that can be performed—needle knife sphincterotomy (precut sphincterotomy) or pull wire sphincterotomy. Needle knife sphincterotomy is performed when deep selective cannulation is unable to be obtained, and can be done over a previously placed stent or guide wire, or when an impacted common bile duct (CBD) stone is protruding through the ampulla ([Fig. 5-31](#)). This technique is more technically challenging and also has a higher risk of bleeding, pancreatitis, and perforation. Pull wire sphincterotomy, conversely, requires deep selective cannulation with or without previous wire placement ([Figs 5-32 and 5-33](#)).
FIGURE 5-31 An impacted common bile duct stone seen extruding through the ampulla. This is best treated by needle knife sphincterotomy to allow release of the stone.
FIGURE 5-32 Following deep selective cannulation of the bile duct, a sphincterotomy is performed with a pull wire sphincterotome.
Indications for sphincterotomy include treatment of sphincter of Oddi dysfunction (SOD), improved access for stone removal or stent placement, and recurrent pancreatitis. To perform sphincterotomy, the pull wire is tightened, bowing it against the papillary roof. Current is then applied while maintaining gentle upward force on the wire and gently lifting the sphincterotome, making the incision in small increments.

**MANAGEMENT OF CHOLEDOCHOLITHIASIS**

In expert hands, over 90% of bile ducts can be successfully cleared of calculi with balloon catheters or Dormia baskets, resulting in an overall ductal clearance rate approximating 85% (Figs 5-34 and 5-35). Stone size is often a limiting factor, as stones greater than 2 cm in diameter often require fragmentation prior to removal. The other reasons for unsuccessful ERCP include patient intolerance, inability to identify or access the papilla, and...
inability to selectively cannulate the desired duct.

**FIGURE 5-34** ERCP radiographic image of a distal common bile duct stone.
FIGURE 5-35 Following sphincterotomy (seen in the upper right-hand portion of the image) and balloon sweeping, the extracted common bile duct stone is seen in the duodenum.

MANAGEMENT OF ACUTE CHOLANGITIS

Endoscopic biliary drainage has now been clearly shown to be the procedure of choice for patients with acute suppurative cholangitis. In critically ill patients, simple endoscopic stenting or nasobiliary drainage, with or without sphincterotomy, should be performed. Complete clearance of the duct is not necessary as long as drainage had been achieved. Stone extraction can be performed after the patient has stabilized, at the time of stent removal 4 to 6 weeks later.

MANAGEMENT OF ACUTE GALLSTONE PANCREATITIS
Patients with biliary pancreatitis can typically be managed conservatively, saving ERCP for patients with worsening pancreatitis or concomitant evidence of biliary obstruction secondary to choledocholithiasis. In these cases, early ERCP and sphincterotomy can significantly reduce morbidity and mortality. In patients who are not an operative candidate for a cholecystectomy, ERCP and sphincterotomy are effective in minimizing the risks of pancreatitis.

ENDOPROSTHESIS INSERTION

Currently available endoprostheses or stents vary in their composition, shape, size, length, deployment system, and method of anchorage. The indications for stent insertion include cholangitis, benign/malignant biliary or pancreatic duct stricture, biliary or pancreatic duct leak, retained/unremovable CBD stones, and prophylactic pancreatic duct stent placement for pancreatitis protection. In patients with biliary fistulae, the goal of the stent is to equilibrate the biliary and duodenal pressures to facilitate closure of the leak (Figs 5-36 to 5-38).

![ERCP revealing extravasation of contrast from an accessory bile duct](image-url)
duct leak.

**FIGURE 5-37** Following a 6-week course of biliary stenting, the leak has resolved.
FIGURE 5-38 Transpapillary biliary stent placement for treatment of the biliary leak.

Straight plastic biliary stents are temporary and must be changed every 3 to 6 months. Obstructive jaundice and cholangitis are common sequelae of occluded stents. Placing multiple stents may increase the length of overall patency, as bile can traverse around and between the stents even if the stent lumen becomes obstructed. SEMS carry a longer patency rate of 9 to 12 months as compared to plastic stents. Uncovered metal stents are less likely to migrate as compared to covered ones, but have a shorter patency rate due to the allowance for ingrowth of tissue or tumor. Newer fully covered self-expanding metal biliary stents also allow for delayed removal and can therefore be used in the management of chronic benign strictures.

Patients undergoing endoscopic palliation for obstructive jaundice secondary to malignancy who are not operative candidates may be better served with SEMS rather than plastic stents due to the decreased need for repeat endoscopic intervention in patients with a limited life expectancy. If patients have both a biliary and duodenal obstruction secondary to
malignancy, it is important to place the biliary SEMS prior to the duodenal stent because access to the papilla becomes very challenging. Palliation of unresectable malignant biliary obstruction in elderly high-risk patients appears to be one of the most significant indications for biliary endoprostheses (Fig. 5-39).

**FIGURE 5-39** Distal common bile duct stricture secondary to a pancreatic head malignancy.

In addition to biliary disorders, ERCP has been employed in the management of benign and malignant pancreatic disorders (Figs 5-40 and 5-41). Pancreatic duct stenting can be used successfully to decompress the ductal system, to bypass ductal leaks and strictures, and to treat pancreatic fistulas. Patients with pancreatic divisum may be treated with minor papilla stenting or sphincterotomy.
FIGURE 5-40 Radiographic image of a pancreatic duct wire prior to stent placement.
FIGURE 5-41 Temporary plastic 5-Fr pancreatic stent in place.

ENDOSCOPIC PSEUDOCYST DRAINAGE/NECROSECTOMY

The management of pancreatic pseudocysts and necrotic debris is one of the more recent advances in the therapeutic armamentarium of the endoscopist. Pancreatic pseudocysts can be approached in a transpapillary or a transvisceral fashion based on the location and nature of the pseudocyst. Many pseudocysts have direct connection to the main pancreatic duct and are referred to as “communicating” pseudocysts. If wire access can be obtained via the pancreatic duct into the cyst cavity, a pancreatic stent can be placed to allow for drainage of the cystic cavity. Although this may result in initial resolution of the cyst, a high recurrence rate exists due to the continued communication to the ductal system. After drainage, subsequent stenting of the pancreatic duct across the site of leakage may be required.
Pancreatic pseudocysts directly adjacent to an endoscopically approachable lumen (ie, stomach, duodenum) may be amenable to a transvisceral approach. Assuring maturity of the cyst, absence of concern for neoplasm, and no evidence of actual infection are important factors to determine prior to endoscopic drainage. The use of EUS is an invaluable adjunct to this procedure for several reasons. It can rule out intervening organs or vasculature, determine if there is extensive debris rather than simple fluid collections, and assure proximity of the cyst to the selected viscus. EUS aspiration followed by guide wire placement is followed by tract dilation and eventual pigtail stent placement. Stents are removed in 6 to 12 weeks after confirming resolution of the pseudocyst.

Patients with pancreatic necrosis rather than simple pseudocyst formation have also been approached endoscopically. Similar to transvisceral cyst drainage, EUS guidance is used to confirm the presence of a collection of debris, and following tract dilation, the endoscope is advanced directly into the adjacent cavity. Tissue is then removed using a combination of irrigation/suction and snare/basket tissue debridement. Stents are placed to maintain the tract to allow for serial debridement of the necrotic tissue.

Recently lumen-apposing, covered, self-expanding metal stents (LACSEMS) have been used for endoscopic drainage of pseudocysts. Intermittent debridement can be done through them as well. Fully covered metal stents have been used as well but may end up being replaced by the LACSEMS as more experience is obtained with them. Initial data from small case series show that they can have a high technical success rate of over 90% in appropriately selected patients and successful drainage in over 90% as well. However, there are some recent reports that describe concerns with bleeding. There are also published data that show that these stents may be no better than plastic stents, so the jury is still out on lumen-apposing metal stents.

**Complications of ERCP**

**POST-ERCP PANCREATITIS**

The occurrence of ERCP-induced pancreatitis is associated with both procedural factors and patient factors. Although the precise factor leading to
postprocedural pancreatitis has yet to be elucidated, many factors including complex interventions such as manometry, multiple pancreatic cannulations or injections, excess delivery of thermal energy, and placement of covered SEMS have all been implicated. Prophylaxis with antibiotics, steroids, somatostatin, xanthine oxidase inhibitors, and immunologic agents such as interleukin-1 have been investigated in multiple prospective comparative trials without success in reduction of pancreatitis. Patient factors associated with pancreatitis include SOD, idiopathic pancreatitis, and the prior history of acute or chronic pancretitis. The use of short-term prophylactic pancreatic stent placement may eventually be proven beneficial in patients following higher risk procedures or who have comorbid disease states that increase their risk for post-ERCP pancreatitis.

Bleeding following endoscopic sphincterotomy occurs in approximately 1% of all cases and can occur immediately or up to 2 weeks after procedure. Hemorrhage should be initially managed by repeat endoscopic intervention. Injection sclerotherapy, balloon tamponade, and endoscopic clip placement are the most common and effective ways to manage this complication. If unsuccessful, angiographic embolization should be used before proceeding to surgical intervention.

Perforation is the least common complication and may occur secondary to the ERCP intervention (wire placement, cannulation, or sphincterotomy) or the actual advancement of the endoscope. Endoscope-induced perforations can occur at the level of the cervical esophagus due to the blind nature of the initial passage of the side-viewing endoscope, or in the duodenum, usually on the lateral aspect opposite the papilla. Proximal esophageal perforations usually can be managed with antibiotics, NPO status, and cervical drainage as needed. Duodenal perforations secondary to the endoscope may result in a large rent of the lateral wall and may require more aggressive therapy including surgical drainage or, in more serious situations, duodenal diversion techniques.

Perforations secondary to ERCP manipulations may occur in the periampullary duodenum or in the biliary tree. Perforations of the bile duct secondary to guide wires or catheter systems are rare but can result in bile peritonitis. Small perforations and leaks in patients without clinical deterioration can usually be managed with transpapillary stent placement and image-guided peritoneal drain placement as needed. CT scans are vital in the
management of these patients. Microperforation of the duodenum can lead to extensive retroperitoneal, intraperitoneal, mediastinal, and subcutaneous air, which appears very concerning, but as long as the patients are clinically stable, this situation can routinely be managed conservatively with antibiotics, NPO status, and close observation. Conversely, patients identified to have retroperitoneal or intraperitoneal fluid collections will most likely require aggressive drainage via either surgical or image-guided techniques. Emergent resective therapy (pancreaticoduodenectomy) should be avoided in these situations.

SMALL BOWEL ENTEROSCOPY

Up until recently, the small bowel had been an elusive part of the gastrointestinal tract in terms of diagnostic and therapeutic endoscopic intervention. The advent of capsule endoscopy has permitted the endoscopist to obtain recorded images of the lumen of the small bowel for identification of obscure sites of bleeding, inflammatory changes, and neoplasia. Unfortunately, there was no potential for tissue sampling or providing therapy. This deficiency has now been addressed with the progression of deep bowel enteroscopy.

Previous endoscopic approaches to evaluate the small bowel included Sonde enteroscopy and push enteroscopy. Both of these were very challenging, time-consuming, often unsuccessful, and provided limited alternatives for therapy. Intraoperative enteroscopy, either transoral or transanal, allowed for the manual pleating of the small bowel on the enteroscope, but was also very challenging. Therapy would be provided surgically after the offending site was identified endoscopically. Intraoperative endoscopic evaluation of the small bowel can also be performed via an enterotomy in the midportion of the bowel allowing the endoscope to be advanced both proximally and distally. One of the undesired consequences of intraoperative endoscopy is massive bowel distention. The use of carbon dioxide (CO\textsubscript{2}) insufflation rather than air insufflation has been shown to minimize the overall distention and length of time for resolution of this problem. Many endoscopists are looking to use CO\textsubscript{2} for all endoscopic interventions, especially those that are expected to be of longer duration.

Several new endoscopic systems have been developed and used for the
evaluation and treatment of small bowel disease. Double-balloon endoscopy and single-balloon endoscopy have allowed the endoscopist to fully evaluate the small bowel, obtain tissue samples, and provide therapy for processes such as bleeding, obstruction, and occult neoplasia.\textsuperscript{128-136} In addition, in patients following surgical resection and reconstruction (ie, Roux-en-Y bypass, long afferent limb), balloon enteroscopy can allow access into the desired segment of the small bowel.\textsuperscript{133}

**LOWER GASTROINTESTINAL ENDOSCOPY**

The field of therapeutic lower endoscopy originated in 1975 when Shinya and Wolff reported the first series of colonoscopic polypectomies.\textsuperscript{137} This groundbreaking report transformed colonoscopy from a purely diagnostic tool into an interventional modality. Since then, therapeutic colonoscopy has expanded to include resection of large neoplastic lesions and stenting for management of strictures, obstructions, and bleeding. Advances in instrumentation and technique will continue to broaden the applications of interventional colonoscopy, possibly even using the colon as a portal to the peritoneal cavity.

**Indications**

Screening colonoscopy has become the standard of care for evaluation of average-risk patients over the age of 50.\textsuperscript{138-141} Prior screening tools such as fecal occult blood testing, sigmoidoscopy, and digital rectal exams no longer are considered effective screening tools.\textsuperscript{142} CT colonography, however, has gained some support due to improved abilities to identify colonic neoplasia; however, smaller lesions are still somewhat a challenge for this imaging tool. The indications for colonoscopy are listed in Table 5-6.

<table>
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<th>TABLE 5-6: INDICATIONS FOR COLONOSCOPY</th>
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**Diagnostic**
1. Evaluate and confirm radiographic findings
2. Identify suspected polyps
3. Unexplained gastrointestinal bleeding or iron deficiency anemia
4. Colon cancer screening and surveillance
5. Follow-up after intervention for polyp or cancer
6. Surveillance of inflammatory bowel disease
7. Significant unexplained diarrhea
8. Preoperative/intraoperative localization of lesions

**Therapeutic**
1. Control bleeding
2. Polypectomy
3. Remove foreign body
4. Reduce sigmoid volvulus
5. Decompress pseudo-obstruction (Ogilvie’s)
6. Dilate or stent strictures/stenoses (malignant and benign)


**Contraindications**

The contraindications for colonoscopy are in part similar to those for EGD and are related to the patient’s associated comorbidities, underlying gastrointestinal disorders, or inability to tolerate conscious sedation. As with EGD, recent myocardial infarction, pneumonia, and recent colorectal surgical procedure are relative contraindications for colonoscopy, and the risks and benefits need to be weighed on an independent basis for each patient to determine appropriateness. A recent surgical anastomosis is most likely safe at any time during the postoperative period to be evaluated endoscopically, remembering that tissue strength will be weakest on postoperative days 5 to 7.

Coagulopathy secondary to thrombocytopenia, liver failure, renal failure, or exogenous use of anticoagulants and platelet-inhibiting agents is a relative contraindication for a diagnostic colonoscopy but an absolute contraindication for a therapeutic intervention. Patient noncooperation and the inability for a patient to be safely sedated due to high cardiopulmonary risk are also contraindications to colonoscopy. Respiratory depression secondary to medications and inability to maintain an airway can occur in
these high-risk patients even though there is no transorally placed scope. Preassessment with ASA classification and Mallampati scores will help predict this high-risk group. Patients with suspected perforation, ischemic colitis, acute diverticulitis, or toxic megacolon should not undergo colonoscopy unless there are plans to provide immediate therapy such as endoscopic closure or stent placement or surgical intervention.

Patient Preparation

Most endoscopic evaluations of the lower gastrointestinal tract can be done under conscious sedation on an outpatient basis. Unsedated colonoscopy can be performed safely but requires a compliant, nonanxious patient, who understands that prior abdominal surgery as well as female gender increases the need for conversion to sedated endoscopy.

The day before the examination, the patient should begin a light diet with only clear liquids at lunch. The most common bowel preparation for colonoscopy uses a sodium sulfate–based electrolyte solution containing polyethylene glycol as an osmotic agent (eg, GoLYTELY). Alternative regimens including magnesium citrate and multiple enema solutions have also been described. In addition to different agents for prep, endoscopists have also used varied timing for preps with the use of split doses, with the final dose being given 4 hours before the scheduled procedure. Fleet Phospho-Soda, a small-volume prep, is no longer an alternative due to the rare occurrence of cardiac complications, but there are other small-volume preps available.

Prophylactic antibiotics are usually not required for colonoscopy. Although diagnostic procedures can be performed in patients on anticoagulative therapy, these medications should be withdrawn if polypectomy or other therapeutic procedures are expected to be performed. Aspirin therapy, unlike other anticoagulative medications, probably does not alter the risk of postpolypectomy bleeding.

Basic Endoscopic Techniques—Colonoscopy

When performing colonoscopy, there are several universal principles to the technique similar to upper endoscopy, but there are also several specific
caveats to assure performance of a safe procedure. Due to the tortuosity of the colon and the lack of fixation, manipulations such as scope torqueing, loop reduction, patient position changes, and abdominal wall manual pressure are vital to the performance of colonoscopy. One other difference from upper endoscopy is the lack of reliability of correlation of shaft length inserted and actual anatomic position in the colon. Therefore, understanding specific colonoscopic landmarks is very important to interpreting actual lower gastrointestinal anatomy. In addition, surgical alterations to the anatomy must be recognizable (Fig. 5-42).

![Image of endoscopic view of the colon](image)

**FIGURE 5-42** An end-to-end stapled anastomosis at the rectosigmoid level is seen in this image.

A digital rectal examination should always be performed prior to initiating the colonoscopic exam. This provides lubrication of the anal canal, relaxes the anal sphincters, provides evaluation of the prostate and lower rectal vault, and assesses the patient’s level of sedation. The endoscope is introduced either by direct straight insertion or by rubbing the tip of the endoscope along the perineal body with the right index finger. Once reaching the anal verge,
the tip of the endoscope is directed into the anal canal.

Once in the rectal vault, insufflation is initiated to allow view of the lumen. Although mucosal inspection occurs during advancement, principal evaluation for pathology occurs on scope withdrawal after the cecum is reached. Gentle advancement of the colonoscope is now performed. If the lumen is lost to view, termed a “red out,” the scope is slightly pulled back and the wheels deflected in combination with scope torque to reestablish the lumen. Passage of the scope into the sigmoid colon can be challenging in patients with prior abdominal surgery, morbid obesity and a large pannus, or multiple diverticula (Fig. 5-43). Abdominal compression and patient position change to supine may assist in this maneuver. Rarely, a “slide-by” maneuver is required to overcome the tight angulation in and out of the sigmoid colon. This technique entails careful insertion without complete luminal view but with appearance of the mucosa sliding by the scope. During all portions of the colonoscopy, however, increased patient discomfort, “redded out view,” and excessive scope resistance with advancement are markers to the endoscopist to pull back one’s colonoscope.

FIGURE 5-43 Multiple diverticula seen in the sigmoid colon.
Exiting the sigmoid colon may require building up a “loop.” This may lead to increased patient discomfort and may require additional medication. Once access into the descending colon is achieved, the loop is reduced by gentle withdrawal and slight torqueing of the scope. Adding variable stiffness to the scope, if available, will now allow advancement in a 1-to-1 fashion to the splenic flexure; 1-to-1 refers to equal scope tip advancement with scope insertion. The descending colon is usually quite straight, and the splenic flexure is identified by the extraluminal blue hue as well as the tight turn encountered as one enters into the distal transverse colon. Suctioning and scope withdrawal will assist in maintaining positioning beyond the splenic flexure.

Introduction of the scope, again with the addition of variable stiffness, should allow 1-to-1 progress through the transverse colon, which is easily identified by the triangular configuration. As one proceeds toward the hepatic flexure, the blue hue of the liver becomes apparent. At this time, paradoxical motion routinely will occur with scope introduction. Access into the ascending colon usually requires the endoscopist to make a sharp deflection at the hepatic flexure followed by withdrawal of the scope and simultaneous suctioning. The ascending colon may have a yellow discoloration due to the continued passage of succus entericus despite a complete bowel preparation. Asking the patient to take a deep breath as well as placing them in supine position may assist in this maneuver. Eventually, the cecum is identified by the ileocecal valve, appendiceal orifice, cecal strap, abdominal wall transillumination, and right lower quadrant palpation (Figs 5-44 and 5-45). Intubation of the ileum, however, is the only way to confirm 100% that you have actually reached the cecum. The terminal ileum can be intubated by deflecting the tip toward the ileocecal valve, gently withdrawing the scope, and prying open the upper lip of the valve. Throughout this maneuver, air insufflation is used. The scope is then slowly advanced into the terminal ileum.
FIGURE 5-44  The cecum is seen here, identified by the ileocecal valve, appendiceal orifice, and classic cecal strap.
FIGURE 5-45 Classic lipomatous appearance of the ileocecal valve helps differentiate it from other colonic folds.

The goal of the endoscopist is to reliably and safely gain access into the cecum, confirming one’s position, and then performing a slow careful withdrawal evaluating the entire mucosal surface. Areas of excess stool must be flushed clear, and extra care must be taken at the flexures and around larger folds to investigate for underlying disease. Retroflexion of the endoscope, which had been used for evaluation of the rectal vault, is now being performed with some regularity in the cecum and flexures, as well as to see behind larger folds. Manipulation by patient position change, as with upper endoscopy, may aid in visualization of areas with excess stool. Retroflexion in the rectum can be done at the beginning or at the end of the procedure (Fig. 5-46). The colonoscope is withdrawn into the anal canal and then carefully advanced for several centimeters. Full upward deflection along with clockwise torquing and gentle advancement will result in the scope looking back toward the distal rectum and dentate line.
Complications

Complications specifically related to colonoscopy include hemorrhage and perforation. The former is most unusual following diagnostic colonoscopy, occurring in 0% to 0.07% of cases. Hemorrhage in this setting is usually intra-abdominal such as following injury to the colon mesentery or to the capsule of the spleen, resulting from the use of excessive force during manipulation. Hemorrhage is seen more often following polypectomy (1%-3%). Postpolypectomy bleeding can be immediate or delayed and can occur up to 2 weeks after the procedure. Repeat colonoscopy is recommended for hemodynamic instability, transfusion requirement, and continued or recurrent episodes of bleeding.

Perforation is the most common complication of colonoscopy, occurring in <1% of cases. These injuries are caused by mechanical or pneumatic pressure and are most common at the rectosigmoid or sigmoid–descending
colon junctions along the antimesenteric border at the site of scope looping. Alternatively, cecal perforation can occur if the colon is excessively insufflated across a more distal nontraversable obstruction. In patients with a competent ileocecal valve, there is a resultant trapping of air between the distal obstruction and the valve, which prevents release of the insufflated air into the small bowel.

Therapeutic colonoscopy can also be complicated by perforation, at the site of therapy, as well as the other previously reported sites. Reported incidences are rare (<1%), with the greatest risks occurring with the removal of sessile polyps. Following polypectomy, patients occasionally develop localized pain secondary to peritoneal irritation, along with fever, tachycardia, and leukocytosis. There is usually no evidence of diffuse peritonitis or overt perforation (ie, no “free air”). This syndrome has been labeled postpolypectomy syndrome and is probably attributable to a transmural electrocoagulation injury with microperforation. Patients usually can be managed conservatively with antibiotics, analgesics, and close observation with serial exams. Symptoms usually resolve within 48 to 72 hours and rarely are surgical interventions needed.

In patients with a suspected perforation, CT studies are recommended to evaluate for abscess formation or intra-abdominal fluid collections. Intra-abdominal fluid collection is a more concerning finding, and these patients require close observation with a low tolerance for surgical intervention. It is important to base therapy on individual patient status, however, rather than just radiographic studies. The presence of intraperitoneal or retroperitoneal air in the absence of clinical peritonitis or hemodynamic instability does not warrant surgical exploration. Perforations that are recognized at the time of a colonoscopy, especially smaller ones after therapeutic intervention such as polypectomy, can be closed with regular hemostatic clips, over-the-scope clips such as the Ovesco overclip, or endoscopic suturing such as with the OverStitch, which have been described earlier in the chapter. The reach may be limited to more distal colon for the OverStitch.

**Polypectomy**

By far, the most commonly performed colonoscopic intervention is polypectomy. When performed at regular intervals, removing adenomatous polyps has been shown to significantly reduce the incidence of colon
Small sessile lesions are amenable to hot or cold biopsy polypectomy. For hot polypectomy, standard biopsy forceps without spike are attached to an electrocautery unit set at 10 to 20 W. The polyp is grasped and lifted from the surrounding mucosa, and monopolar cautery is applied in short bursts until the base of the polyp whitens. The biopsy forceps are sharply withdrawn and the polyp is then removed through the working channel of the colonoscope. Polypectomy serves to biopsy the polyp and ablate any residual tissue, thereby diminishing the risk of progression to carcinoma. Due to the concern for delayed bleeding following sloughing of the eschar as well as the risk of perforation, many endoscopists are now adopting cold polypectomy techniques. Several series have shown no difference in the rates of bleeding, and it presents a more easily evaluable specimen to the pathologist without cautery artifact.

Pedunculated polyps are suitable for snare polypectomy (Fig. 5-47). The base of the polyp is encircled with the snare several millimeters below the head-stalk junction. This allows removal of a portion of the stalk for pathologic evaluation to rule out invasion of the lamina or muscular layers, identifying a more advanced neoplasm. Cautery is applied as the snare is gradually closed, thus severing the polyp and cauterizing the base. Broader-based pedunculated polyps may be managed with placement of an endoscopic pretied endoloop proximal to the site of resection to help minimize bleeding. These loops usually will slough off within several weeks and pass spontaneously.
Sessile polyps are frequently more difficult to manage than pedunculated polyps. Small sessile lesions may be captured in a single application of a snare and resected, with (hot) or without (cold) cautery, while larger lesions might require resection in a piecemeal fashion. Piecemeal resection provides for removal of a larger lesion along with ablation of residual tissue, but may make pathologic interpretation more challenging.\textsuperscript{144}

Resection of sessile polyps poses a higher risk of colonic perforation than pedunculated polyps. Given that, EMR has been developed to minimize the risk of perforation and ensure complete resection of the lesion. This is provided by submucosal injection of saline to create a cushion between the mucosa and muscularis to help minimize the risk for perforation.\textsuperscript{144-147} Lesions that do not easily elevate may have a component of invasive carcinoma, and these tumors should be biopsied and tattooed, rather than attempted to be endoscopically resected. Following removal of large sessile lesions, APC ablation of the site has been proposed to minimize adenoma
POLYP RETRIEVAL

Small polyps may be retrieved through the suction channel of the endoscope and captured in a trap. Larger polyps may be recovered in a net placed through the working channel of the endoscope or apposed to the tip of the endoscope by constant application of suction and then withdrawn with the scope. Marking the site of resection with a carbon particle–based tattoo via a sclerotherapy needle will allow for more accurate surveillance, as well as to guide surgery if the polyp proves to be malignant. Injections should be placed at multiple sites circumferentially to allow for the most reliable visualization at the time of surgery or during subsequent surveillance endoscopy.

POLYP SURVEILLANCE

Over the past 15 years, much has been learned about the nature of the adenoma carcinoma sequence, leading to ongoing changes in the recommendations for polyp surveillance. Average-risk patients with satisfactory bowel preps require repeat surveillance in 10 years, while patients with poorer preps might be recommenced to have a shorter interval of 5 to 7 years. Hyperplastic polyps carry an undetermined risk for and association with advanced neoplasia, although there has been some suggestion that left-side hyperplastic lesions have a more aggressive nature than those in the rectosigmoid. Similar to fundic gland polyps of the stomach, these lesions may be sampled but do not need to be fully removed. Tubular adenomas, tubulovillous adenomas, and villous adenomas warrant a surveillance colonoscopy at 5, 3, and 1 year, respectively.

EMR and ESD in Colon

Significant advancement in endoluminal techniques for colorectal application has been made since the turn of the century. Increased implementation of techniques such as EMR and ESD has given the surgical endoscopist additional noninvasive tools to safely treat increasingly difficult benign and malignant colorectal lesions. EMR has its origins in Japan for the treatment of early gastric cancer, with subsequent implementation in Western nations...
for benign diseases such as Barrett esophagus with dysplasia and gastrointestinal adenomas.\textsuperscript{148,149} Technically challenging lower GI lesions such as flat and large sessile polyps not amenable to snare polypectomy have historically caused endoscopists great strife, leaving surgical referral as the only option after incomplete resection due to the elevated risk of malignancy harbored in such polyps. Yet with the knowledge that neoplastic lesions with <1 mm of submucosal invasion are unlikely to have lymph node metastases, endoscopic methods that allow adequate resection of these lesions have become increasingly valuable by saving the resources and morbidity associated with a surgical procedure that would otherwise be necessary.\textsuperscript{150} EMR is indicated for lesions that are limited to the mucosa and <2 cm in size, although it has been successfully used even for much larger cancers and adenomas. Although EMR can be used to obtain pathologic samples for diagnosis, prior biopsy showing intramucosal carcinoma or adenoma often precedes performance of an EMR procedure with curative intent.

The endoscopic appearance of lesions can give valuable information predicting a lesion’s depth of invasion, likelihood to harbor underlying malignancy, and thus, expected utility of performing EMR of the lesion. The Paris classification system (Table 5-7) provides a standardized way of categorizing nonpolypoid lesions, and lesions classified as Is or Ip typically are not included in EMR literature because these can often be treated by snare polypectomy. The appearance of associated colonic pit patterns has been shown to correlate with underlying histopathologic structure (Table 5-8) and, with the help of magnified colonoscopy, can be used to identify candidate lesions for EMR.\textsuperscript{151,152} Chromoendoscopy serves as a diagnostic adjunct by using a diluted stain like Lugol’s solution (UGI) or 0.1% to 0.5% indigo carmine that collects within mucosal depressions to highlight the surface abnormalities and borders of lesions that are otherwise difficult to appreciate, making resection margins easier to identify. This is usually done via dye injection through a separate working port prior to lifting of the lesion as described subsequently. Magnified colonoscopy using NBI has shown similar efficacy as chromoendoscopy in determining pit patterns and discerning neoplastic lesions.\textsuperscript{153}
Although general anesthesia may be used, EMR can typically be easily performed under moderate sedation using fentanyl or midazolam. Full-thickness resection of the affected mucosa down to the middle or deep submucosal level is implied with EMR and can be accomplished via one of a few available techniques, including injection-assisted EMR, strip biopsy, EMR-C (special cap), and ligation-assisted and underwater EMR. The common principle of these variable methods is to provide some separation of
the superficial lesion from the deeper submucosal layer(s) before ensnaring and removing it with an energy source. The most common method, injection-assisted EMR, is based on the work of Kudo and involves a 5- to 50-mL injection of some aqueous solution into the loose connective tissue of the submucosal layer, providing a lifting cushion that facilitates full inclusion of the lesion during subsequent snare polypectomy. The injection is typically begun at the most distal part of the lesion from the colonoscope, and normal saline is the most common solution but may be limited by rapid absorption requiring multiple injections, leading to investigative use of other solutions such as glycerol, hyaluronic acid, fibrinogen-based products, and even autologous blood. Strip biopsy, also called the “injection-lift-cut” technique, entails grasping the lesion to be removed on tension before ligating it. This method is used less frequently because it commonly leaves pieces of the lesion remaining that must be subsequently removed piecemeal by methods such as APC or hot biopsy forceps. EMR-C incorporates a special capped snare that opens at the distal cap end where tissue is aspirated before the snare tightens and the lesion excised with cautery. However, EMR-C been associated with increased risk of perforation, and its use is now limited primarily to the rectum because of its extraperitoneal location. Ligation-assisted EMR involves the placement of 1 or more bands in similar fashion to banding for variceal bleeding to isolate the mucosa and submucosa with or without submucosal injection prior to snare polypectomy. In underwater EMR, luminal air is replaced by 500 to 1000 mL of water, and the mucosal/submucosal layers “float” away from a muscularis propria that remains flat while immersed, allowing for snare excision without submucosal injection. This technique has the theoretical advantage of avoiding inadvertent introduction of neoplastic cells into deeper tissues, and some studies suggest improved rates of complete resection and diminished recurrence compared to classic lifting techniques. One primary risk of EMR is bleeding, ranging from 0% to 22% according to literature and rarely significant enough to require reintervention, whereas perforation remains a rare complication with an incidence of less than 0.2%. Recent studies show that placement of hemoclips at the time of EMR for large polyps effectively diminishes risk for clinically significant delayed bleeding from 9.7% to 1.8% compared to unclosed defects. For lesions that are too large or otherwise difficult to remove en bloc with EMR, ESD may be employed as
an alternative to invasive surgical resection.

ESD was first used on local gastric cancers >2 cm but has more recently been successfully applied to similar lower gastrointestinal tract lesions. In comparison to UGI applications, anatomic factors of the colorectum, including thinner walls, more complex tortuosity, narrow lumen, and longer relative length, make ESD in this location more technically challenging and risky and thus limit the breadth of its implementation. Colonic ESD is primarily performed by experts in Japan, where the Japan Colorectal ESD Standardization Implementation Working Group has concluded “that any lesion difficult to remove en bloc should be considered a candidate for ESD.” Candidate lesions have been further defined as those that are large in size (>2 cm) or pseudodepressed lateral-spreading tumors, 0 to I lesions or those with a VI-type pit pattern with adenocarcinoma suspected, recurrent lesions after EMR, carcinoma with less than 1000 μm of submucosal penetration, postbiopsy mucosal lesions with fibrotic changes, or an adenoma that exhibits a nonlifting sign (insufficient mucosal lifting after injection, signifying adhesion of some etiology to the deeper underlying layers of the bowel wall).

ESD employs similar equipment to EMR, including injection solution, a high-frequency power supply, a transparent tip to produce adequate submucosal tension, an electrosurgical device, and hemostatic forceps. Several electrosurgical devices are available for ESD and generally fall into 1 of 2 larger categories—needle knife (single instrument capable of injection and dissection) or grasping (scissors) type—the details of which are beyond the scope of this text and can be found elsewhere. The most common ESD procedural sequence begins with submucosal elevation and injection followed by mucosal incision with a hook knife, circumferential submucosal dissection with an insulated tip knife for en bloc resection, and completion of wound bed hemostasis with a small cup hemostatic forceps. With the deeper level of dissection, perforation is the most feared complication and occurs more frequently than with EMR, with a reported incidence of 4% to 10% in the colon and 6% to 18% in the rectum. Bleeding rarely occurs with colonic dissections, with an incidence of 0% to 2%, but remains a significant risk during rectal dissection, occurring in 13% to 28.6% of cases. Altogether the data suggest that ESD may only be safe and appropriate for resection of colonic and not rectal polyps, which is likely to
be supplanted for such application by the advent of transanal endoscopic microsurgery.

**Lower Gastrointestinal Bleeding**

Sources of lower gastrointestinal bleeding include UGI bleeding, infection, ischemia, neoplasia, diverticulosis, angiodysplasia, and anorectal disease. A detailed history of the nature of bleeding is vital to the management of patients with lower gastrointestinal bleeding, identifying underlying coagulopathy, recent surgical or colonoscopic interventions (polypectomy), and associated comorbid diseases. Blood is a very active cathartic, and colonoscopy can be performed in the unprepared colon with extensive bleeding. Otherwise, a rapid prep over 3 to 4 hours can be used in patients with less aggressive bleeding prior to endoscopic evaluation. The endoscopist must compare the need for a more urgent intervention versus the necessity of a more adequately cleared mucosal surface.

Colonoscopic therapy for lower gastrointestinal hemorrhage within 6 to 24 hours of admission has been shown to diminish rates of rebleeding and reduce the necessity for urgent surgical intervention. Various methods are available for hemostasis including thermal and nonthermal devices and are described in the preceding sections of this chapter. One must always remember, however, that the colon wall is thinner, especially on the right side, as compared to the stomach. Depth of penetration of the varied thermal endoscopic devices must be closely considered to avoid full-thickness perforations.

Diverticular disease is the most frequent cause of lower gastrointestinal hemorrhage. Up to 75% of diverticular bleeds are self-limited, but in patients with transfusion requirements, massive hematochezia, or hemodynamic instability, colonoscopy may aid in confirming diagnosis, identifying the site, achieving hemostasis, and limiting patient morbidity. Locating the precise site of bleeding may be difficult in the face of multiple diverticula and a blood-stained colon. The bleeding diverticular vessel is frequently at the lip of the diverticulum, although bleeding vessels in the dome of the diverticulum may also occur. The use of endoscopic clips and ligation bands for treatment of bleeding diverticula has also been reported.

Vascular ectasia or angiodysplasia, commonly in the right colon but also...
routinely multicentric, is another common cause of lower gastrointestinal hemorrhage. APC is invaluable in this situation, but care should be taken to avoid excessive distension of the bowel, as the argon gas accumulates and could lead to perforation.\(^{169}\) Other thermal endoscopic contact probes, as described in previous sections of this chapter, can also be used.

**Colonoscopic Decompression**

Mechanical or nonmechanical obstructions with unrelieved distention of the colon, in addition to leading to patient discomfort, can result in bowel ischemia, perforation, and death. In patients with colonic distention secondary to acute pseudo-obstruction, Ogilvie syndrome, colonoscopy provides both a diagnostic and therapeutic potential. Underlying etiologies including ischemia, infectious colitis, or an unsuspected obstructing lesion must be excluded.

Conservative treatment is initially indicated in patients with benign abdominal exams, clinical stability, and cecal diameters less than 12 cm. Patients should be maintained NPO, electrolyte imbalances corrected, narcotics withdrawn, and one should consider possible placement of nasogastric and rectal tubes.

Colonoscopic decompression is done without a routine bowel preparation, thus limiting the overall mucosal evaluation. The endoscope is advanced, with limited air insufflation, as far proximally as can be achieved without excessive bowel wall tension, minimizing any risk for perforation. Decompression is then performed upon withdrawal of the colonoscope, suctioning both fluid and intraluminal air. Although the cecum is the optimal endpoint, successful decompression can also be achieved with a less complete colonoscopy. Evaluation of visualized segments of the colon for ischemia and/or mechanical obstruction, possibly requiring stent placement or dilation, is crucial. It must be understood that repeat colonoscopic decompression is routinely required in patients with pseudo-obstruction, and they should be watched closely for several days.

**Enteral Stents**

Colonic stenting can provide relief of malignant colon obstruction or benign
stricture and serve either as palliation or as a bridge to operation.\textsuperscript{170-175} Permanent SEMT stents are commonly used in large bowel obstruction. TTS stents are placed under endoscopic and fluoroscopic guidance. The malignant stricture is located endoscopically, and a guide wire is passed through the narrowed lumen (Figs 5-48 and 5-49). Contrast is injected into the bowel lumen, typically through an ERCP catheter, to define the borders of the stricture. If possible, the proximal and distal extents of the stricture are marked by injecting submucosal contrast. The stent is then placed over the wire, positioned properly, and deployed (Fig. 5-50). SEMS have shown efficacy in reducing the need for emergency operation in acute large bowel obstruction.\textsuperscript{170,171,173} In patients who are not candidates for operation, metal stents may serve a palliative purpose.\textsuperscript{172} Stenting is generally safe, although perforation has been reported in up to 10% of cases. Migration of stents can also occur, although this is less likely due to tissue in-growth, which can also lead to subsequent stent occlusion.

\textbf{FIGURE 5-48} An obstructing sigmoid colon cancer prior to stent placement.
FIGURE 5-49 Guide wire placement across the obstructing lesion.

FIGURE 5-50 Following stent deployment, obstruction is relieved as seen
by the large volume of liquid stool.

**FUTURE DEVELOPMENTS**

The future developments in endoscopy will be based on advancements of both the tools and the applications available to endoluminal therapy. As surgery becomes less invasive with the advancement of laparoscopy, endoscopy is taking on an increasingly more invasive and therapeutic role. Intraluminal, intramural, and transluminal procedures are being developed with the goal of further supplanting surgery. The interest in natural orifice transluminal endoscopic surgery united surgeons and gastroenterologists with the desire to access the abdominal cavity via naturally existing orifices including the stomach, colon, bladder, and vagina. The obvious limitations to natural orifice transluminal endoscopic surgery were based on the lack of adequate and appropriate endoscopic equipment. The accessories were too flimsy to perform intra-abdominal manipulation of tissue, and the endoscopes were too flexible, inhibiting access and stable positioning once in the abdominal cavity. It was apparent early on that stable platforms would be necessary, along with endoscopic tools for cutting, hemostasis, and tissue manipulation. Scissors, suturing devices, bipolar forceps, and grasping devices are a few of the novel instruments that have been added to the endoscopist’s armamentarium.

These tools, however, will more likely impact intraluminal and intramural endoscopic surgery. The ability to perform full-thickness resection, intraluminal anastomoses, and closure of perforations are all procedures that are on the horizon, and in selected patients at certain centers, some procedures such as POEM and POP are already being done. It is imperative that surgeons stay abreast of the numerous advancements in these technologies.

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FUNDAMENTALS OF LAPAROSCOPIC SURGERY
Fernando Mier • John G. Hunter

The field of minimally invasive surgery has evolved and grown over the past 3 decades. This was made possible by developments in technology and was fueled by patient demands for less painful operations and quicker postoperative recovery.

Minimally invasive approaches are now widely used for gastrointestinal, bariatric, hernia, and solid organ surgery. It is the surgeon’s responsibility to become familiar with the new set of techniques and instruments, as well as knowing when to apply them and when to convert to an open operation. Furthermore, understanding how to use and troubleshoot the equipment used in these procedures is critical for any surgeon who performs minimally invasive surgery.

PREOPERATIVE CONSIDERATIONS

Patient Selection

As in all surgery, choosing the right operation for the patient is the first step.
Since all laparoscopic surgery of the abdomen requires the use of general anesthesia, the ability to tolerate anesthesia is an absolute requirement. Patients with impaired exercise tolerance or a history of shortness of breath will need a preoperative consultation with a cardiologist or pulmonologist. Patients with severe carbon dioxide (CO₂) retention can be difficult to manage intraoperatively because the use of carbon dioxide for pneumoperitoneum exacerbates the condition. By increasing the minute ventilation and decreasing the CO₂ pneumoperitoneum from 15 to 8 to 10 mm Hg, one can control metabolic acidosis. Rarely, when these measures are ineffective at controlling hypercarbia, we have resorted to using nitrous oxide (N₂O) for peritoneal insufflation. While not suppressing combustion (as does CO₂), N₂O supports combustion no more than air and has been proven safe for laparoscopic use. A single, blind, randomized trial has demonstrated that N₂O pneumoperitoneum is associated with decreased postoperative pain compared with CO₂.

When deciding if a patient is a suitable candidate for a laparoscopic procedure, it is important to assess patient or procedure characteristics that will lengthen the operative time sufficiently to nullify the benefits of laparoscopy. If the laparoscopic operation takes substantially longer than the open equivalent or is more risky, then it is not prudent to proceed laparoscopically. A history of a prior open procedure or multiple open procedures can make access to the abdomen difficult and will be discussed in detail later in this chapter. Adhesions and scarring in the surgical field from prior surgery can make laparoscopic surgery very difficult and may require use of many novel dissecting and coagulating tools. Operating on patients with severe obesity is challenging specifically because torque on transabdominal ports leads to surgeon fatigue and diminishes surgical dexterity. In addition, the long distance from the insufflated abdominal wall to the abdominal organs can make laparoscopic surgery a “far reach.” Special long ports and instruments are available to overcome this difficulty.

Inability to obtain an adequate working space makes laparoscopic surgery impossible. This is encountered most commonly in patients with dilation of the intestine from bowel obstruction. Often, laparoscopic lysis of adhesions for distal bowel obstruction is not technically feasible. Some patients with appendicitis will have sufficient small bowel dilation that laparoscopic access to the right iliac fossa is not possible. Many laparoscopic procedures create
working spaces in extraperitoneal locations. An example is the laparoscopic hernia repair usually performed in the anterior preperitoneal space of Retzius; this may require the use of a balloon dissector to create the space followed by low-pressure insufflation. There are fewer physiologic consequences than with a pneumoperitoneum, but CO\textsubscript{2} can spread widely through the soft tissues, causing subcutaneous emphysema.

**Patient Positioning**

We rely on gravity for retraction of the abdominal contents to provide exposure. Sometimes this requires steep positional changes, and care must be taken to prevent nerve complications or neuropathies after laparoscopic surgery as in open surgery. Patients must be positioned properly at the beginning of the procedure, making certain that all pressure points are padded. Peroneal nerve injury is caused by lateral pressure at the knee and may occur when the table is “airplaned” to the side with a retractor holding the patient in place. Femoral and sciatic neuropathies are similar in that they are due to compression. Padding the retractor arms and securing the patient to the table can prevent these neuropathies.

It is best if the arms can be tucked for most laparoscopic procedures so that the surgeon may move freely up and down the table in order to line up instruments and the target tissue. This is most important for procedures in the pelvis, where the surgeon will want to stand adjacent to the contralateral thorax. However, even with upper abdominal laparoscopy, tucked arms allow more optimal positioning of instrument columns and monitors. If there is a need to extend the arms on arm boards, one must be very careful to avoid a brachial plexus injury that occurs when the arm is extended greater than 90 degrees at the shoulder. Usually, at the start of a procedure, the arm positioning is safe, but it may change as the patient slides down on the table. For this reason, when reverse Trendelenburg is expected, we place footplates at the feet. This prevents sliding on the table and does not cause any discomfort to the patient because it is much like standing. We secure the ankles as well to be sure they do not “twist” during the procedure. There are footplates available for split-leg tables that can be used when operating on the upper abdomen and steep reverse Trendelenburg is needed.

There may be an increased incidence of deep venous thrombosis after
laparoscopic surgery that is due to pooling of blood in the venous system of the lower extremities. Venous return is impaired by compression of the iliac veins from the elevated intra-abdominal pressure exerted by the pneumoperitoneum. In addition, the positional effects of placing the patient in a steep reverse Trendelenburg position lead to further distension of the venous system. All patients undergoing laparoscopic procedures in reverse Trendelenburg, even short procedures such as laparoscopic cholecystectomy, should have sequential compression devices placed before the procedure begins, although this does not improve femoral blood flow entirely. Patients at high risk for developing deep venous thrombosis should be treated with subcutaneous anticoagulants as either fractionated or unfractionated heparin. This includes patients undergoing lengthy procedures, patients with malignancy, obese patients, patients with a prior history of deep venous thrombosis or pulmonary embolism, and patients in whom ambulation after surgery will be delayed.

Laparoscopic surgery is associated with a high incidence of postoperative nausea and vomiting. A recent review asserts that serotonin receptor antagonists such as ondansetron (Zofran, GlaxoSmithKline) appear to be the most effective and should be considered for routine prophylaxis. Another prospective, blinded, randomized trial showed a decrease in postoperative nausea and vomiting when low-dose steroids were given to all patients. There was no increased infection rate in the group that received steroids. Other preventive measures include ensuring adequate hydration and decompression of the stomach with an orogastric tube before the end of the procedure. Intravenous nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac provide superb pain relief and diminish the need for postoperative narcotics, which may help to prevent nausea and vomiting.

**INTRAOPERATIVE CONSIDERATIONS**

**Port Placement**

**SITE SELECTION**

Proper placement of ports is important to facilitate completion of the laparoscopic procedure. The location of port sites depends on the type of
procedure; the primary port should be placed with this in mind. We do not always place the primary port at the umbilicus but rather judge which site is best for the camera or which is the safest site for the primary puncture in a previously operated abdomen. The first laparoscopic port can be positioned anywhere in the abdomen after pneumoperitoneum has been created. The additional or secondary ports should not be placed too close to each other. The optimal pattern of port placement should form an equilateral triangle or a diamond array around the operative field. This “diamond of success” takes into account the optimal working distance from the operative target for each instrument and the telescope (Fig. 6-1). In laparoscopy, the standard instrument length is 30 cm. To produce a 1:1 translation and movement from the surgeon’s hands to the operative field, the fulcrum of the instrument should be 15 cm from the target. A similar separation of the 2 working ports (surgeon’s left and right hands) ensures that these 2 instruments will not be involved in “sword fighting” and that the angle between the 2 instruments at the target will be optimal (between 60 and 90 degrees). The secondary port site is chosen, and the abdominal wall is transilluminated to avoid large abdominal wall vessels.\textsuperscript{10,11} The trocar is watched laparoscopically as it enters into the abdomen, and care is taken to avoid injuring the abdominal contents. During the procedure, the area beneath the primary trocar site is inspected for unexpected injuries.
PORT CHARACTERISTICS

There is a wide variety of ports, each with different characteristics, available on the market. The bladed trocars cut the abdominal wall fascia during entry. Because the nonbladed trocars do not cut the abdominal wall as much, they...
make smaller defects in the abdominal wall and may be less prone to hernia formation in the future. The most commonly used bladed ports have a shield that retracts as the blade is pushed through the fascia of the abdominal wall, and then it engages once inside the abdomen. When first introduced to the market, the shields were called safety shields, but they have lost that designation because the shield provides little protection. The nonbladed trocars come in many forms. One nonbladed trocar is used in the Step system (Covidien, Mansfield, MA), a modified Veress needle that locks inside an expandable sheath. Once inside the abdomen, the Veress needle is removed, and a blunt port is passed into the sheath that guides the port by dilating radially. The Ethicon nonbladed trocar has a rough edge of plastic that is twisted and pushed through the layers of the abdominal wall. None of these technologies have proven safer than the more economical reusable nonshielded bladed trocar systems made by most instrument companies (Fig. 6-2).

**FIGURE 6-2** Various trocars for the introduction of laparoscopic ports through the abdominal wall. There are bladed and nonbladed types. Of the bladed trocars, there are shielded and nonshielded types. The Veress needle with a radially dilating sheath used in the Step system is an example of a nonbladed trocar. (Reproduced with permission from Chandler JG, Corson SL, Way LW. Three spectra of laparoscopic entry access injuries, *J Am Coll Surg.* 2001;April;192(4):478–490.)
Important characteristics of a port need to be considered when choosing which port to use. The advantage of a port introduced with a nonbladed trocar is that the abdominal wall defect is smaller, which does not allow gas to leak from the abdomen during the procedure. Because the fascia is not cut, there is a lower risk of port-site hernia, and the fascia of most 10-mm incisions does not have to be closed. In addition, these ports tend not to slip out of the abdominal wall during manipulation. Other considerations when choosing a port are the size of the external component, the smoothness of entry and exit of the instruments and specimens, and whether an external reducer cap is needed.

ACCESS OR PLACEMENT OF THE FIRST PORT

No single access technique has emerged as the safest and best technique. The techniques for abdominal access include direct-puncture and open-access techniques. The direct-puncture technique can be performed either by direct trocar insertion without pneumoperitoneum or by first obtaining pneumoperitoneum using a Veress needle and then inserting the first trocar directly. The latter technique is performed most commonly in the United States. Each technique has a specific pattern of complications that must be considered when choosing among them.

The Veress needle access was first described in 1938. This technique involves direct insertion of a needle into the peritoneum after lifting the abdominal wall with towel clips or a firm grip. The optimal site for insertion of the Veress needle is through the central scar at the umbilicus. One can make either a vertical skin incision through the umbilicus, hiding the incision in the base, or a curvilinear incision in an infraumbilical or supraumbilical position. Nevertheless, insertion of the Veress needle should be aimed at the central scar, where the layers of the abdominal wall are fused. This does not mean, though, that the first port inserted must be at the umbilicus. Advocates state that the benefits of this technique are the ability to place the initial port anywhere on the abdomen, that it is relatively quick, and that the skin and fascial openings are smaller, which prevents CO\textsubscript{2} leakage during the procedure.

For safe Veress needle insertion, first one must be certain to check the stylet and needle patency, especially when reinserting it after an unsuccessful initial pass. The Veress needle is available either as a reusable or disposable
product and comes in 2 sizes, both long and short. The spring mechanism that pushes the stylet out, thus protecting bowel from the needle, must be tested when using the reusable Veress needle.

The safest technique requires stabilizing the abdominal wall (we prefer penetrating towel clips in nonobese patients). It is important to have control over the force and depth of insertion of the needle. This is aided by either placing your wrist against the patient’s abdomen or using the nondominant hand to support the hand wielding the needle. It is sometimes necessary to raise the operating table to achieve the proper control. One must be mindful of the fact that the most common catastrophic complication from Veress needle insertion is injury to major vessels. The trajectory of the needle should not be angled toward the aorta or iliac vessels (Fig. 6-3).

![Proper Veress technique in the left upper quadrant using the dominant hand with the wrist stabilized on the patient. The nondominant hand is used to stabilize the abdominal wall.](image)

**FIGURE 6-3** Proper Veress technique in the left upper quadrant using the dominant hand with the wrist stabilized on the patient. The nondominant hand is used to stabilize the abdominal wall.

After placement of the Veress needle, one should perform an aspiration test by connecting a syringe filled with saline to the top of the Veress needle and aspirate. Aspiration of air, blood, or bile signifies incorrect placement and should prompt serious concern for an unexpected injury. If there is no
aspirate, saline should be injected and should flow easily. The saline should flow down the Veress needle into the peritoneal cavity without pressure, a qualitative measure. Removing the plunger from the syringe and watching the saline level drop briskly may achieve a quantitative assessment of patency. If the saline flows slowly or not at all, the needle is likely in the wrong position, that is, up against an intra-abdominal organ, or it is in the preperitoneal space. Alternatively, the tip may be occluded with fat, or the system may have an “air lock.” To test this, inject a little bit of fluid again gently, and retest by removing the plunger and allowing the saline to drop into the abdomen.

The Veress needle then is connected to the insufflation tubing. The expected initial insufflation pressure, assuming proper placement, should be less than 5 to 6 mm Hg. Abnormally high insufflation pressure is an indication that something is not right.17 Because the insufflator is usually set to allow a maximum pressure of 15 mm Hg, a value greater than this suggests that the patient is not anesthetized adequately and is contracting his or her abdominal muscles. If the insufflator records a pressure of 15 mm Hg, there are a few explanations. The most ominous cause would be incorrect placement into an intra-abdominal organ. More likely, the Veress needle tip may be against omentum or is in the preperitoneal space. The insufflation line may be occluded at the stopcock, or there may be a kink in the tubing.

Direct trocar insertion without first establishing pneumoperitoneum is not used as frequently because many surgeons think that it is dangerous given that the bladed trocar must be pushed into the abdomen with significant force to penetrate the abdominal wall. Surgeons unfamiliar with the technique worry about injury to bowel and vessels when using excessive force. There are, however, many surgeons who perform this technique with no increased complication rate, confirming its safety.18-22 Still other surgeons believe that the open-access technique that involves a “minilaparotomy” is the safest.15,23-25

The open, or Hasson, technique was first described in 1974.15 A 1- to 2-cm skin incision is made at the umbilicus, and the soft tissue is divided to identify the abdominal wall. The fascia and muscles are opened with a knife, and the peritoneum is identified and grasped with Kocher or Allis clamps. A 0-0 absorbable suture is placed through the fascia, and the Hasson port is secured to the fascial sutures. Later, these sutures can be used to close the abdominal wall. The insufflation tubing is attached to the sideport of the trocar, and the abdomen is insufflated rapidly to 15 mm Hg.
Newer trocars, called *optical trocars*, allow visualization of the tip of the trocar as it passes through the layers of the abdominal wall (Fig. 6-4). A straight-viewing 0-degree scope is placed inside a clear trocar that is available with and without a bladed tip. Safe introduction of an optical trocar is a skill that requires judgment and experience and can best be learned in patients with no prior surgery after insufflation is established. Success depends on the operator’s ability to see each of the layers of tissue, although visualization does not imply safety. It is useful for the surgeon to have command of several access techniques because there is no single technique that is best for all circumstances.

![Optical trocar](image)

**FIGURE 6-4** Optical trocar. (All rights reserved. Used with the permission of Medtronic.)

**DIFFICULT ACCESS**
Access can be the most challenging aspect of the procedure in some patients no matter which technique is used. This is especially true in obese patients. First, the site of the central scar is often judged inaccurately because the umbilicus is in a caudad position owing to the loose panniculus. Additionally, there is an increased distance between the skin and the abdominal wall fascia. The Veress needle may not penetrate the abdominal wall. If an open-access technique is chosen, it may be difficult to expose the abdominal wall through a small incision. Degenerated fascia in obese patients will make the abdominal wall bounce against the needle or finger, making its identification difficult. Raising the skin with penetrating towel clips does not facilitate this exposure and, in fact, distorts the anatomy, making it more difficult to identify the fascia. Sometimes a modified technique described by Vakili and Knight can be helpful.28 This is a combination of open and Veress techniques in which a small skin incision is made in obese patients. Kochers are used to hold the abdominal wall fascia up, and a Veress needle is passed through the abdominal wall.

Access is also difficult in patients who have had prior surgery through a midline incision. In these patients, it is unsafe to perform the Hasson technique through the midline site because of the potential for adhesions of bowel to the posterior surface of the abdominal wall. Injury can occur when dividing the fascia or when sweeping adhesions away with a finger. It is difficult to perform the open technique at sites other than the umbilicus because of the multiple layers of the abdominal wall. In these patients, we prefer to place the Veress needle in the next safest location, which is the left upper quadrant along the costal margin. One must be certain that the table is flat because the spleen and liver are injured more easily in patients in the reverse Trendelenburg position. One must be certain that the stomach is decompressed with an orogastric tube before inserting the Veress needle in the left upper quadrant. Once insufflation is obtained, a port can be placed into the abdomen away from the previously operated field. We prefer entering with a 5-mm step port followed by a 30-degree 5-mm scope. Other surgeons recommend use of optical trocars in this situation.

FASCIAL CLOSURE

Care should be taken to prevent port-site hernias, which occur in 0.65% to 2.80% of laparoscopic gastrointestinal operations,29 because they can lead to
bowel obstruction, incarceration, and/or Richter hernias. All defects created with a 10-mm or greater bladed trocar should be closed, although this is not necessary when using some of the newer nonbladed trocars that create smaller fascial defects. Most 5-mm defects do not require fascial closure in adults, although there are reported cases of hernias at these sites. Because there is always a possibility of formation of a port-site hernia, the smallest possible port always should be used. When a port is manipulated excessively or has to be replaced multiple times, there may be a larger than expected fascial defect that may require closure. Additional recommendations are to place ports lateral to the rectus muscles when possible. At the conclusion of the procedure, removal of ports from the abdomen should be observed to be certain that omentum or abdominal contents are not brought up through the abdominal wall.

Fascial closure can prevent trocar-site hernia. A number of port-site closure devices have been developed because small laparoscopic incisions make it difficult to close the abdominal wall with round needles. The closure devices function like crochet needles, passing a suture through the abdominal wall on one side of the fascial incision. The suture end is released intra-abdominally under laparoscopic visualization, and the needle is removed. The needle is replaced (without suture) on the other side of the incision, and the free end is secured and pulled back out through the abdominal wall. A knot is then tied that closes the trocar site, as viewed laparoscopically (Fig. 6-5).
FIGURE 6-5 Using the inlet device, the suture is passed through the abdominal wall on one side of the fascial incision. The suture end is released intra-abdominally under laparoscopic visualization, the suture then is pulled out on the other side of the incision using the device, and a knot is tied.

TROCAR INJURY

The overall risk of a trocar injury to intra-abdominal structures is estimated to be between 5 in 10,000 and 3 in 1000. Almost all injuries occur during primary trocar insertion. According to Chandler and colleagues, the most commonly injured organ is the small bowel (25.4%), followed by the iliac artery (18.5%), colon (12.2%), iliac vein (8.9%), mesenteric vessels (7.3%), and aorta (6.4%). All other organs were injured less than 5% of the time. The mortality from trocar injury is 13%, with 44% owing to major vessel injury, 26% to bowel injury with delayed diagnosis, and 20% to small bowel injury. Major vascular injuries are noticed immediately and require rapid conversion to laparotomy. They are managed by applying pressure when possible to allow the anesthesia team to maintain and correct volume and prepare for
rapid blood loss. Then the surgeon gets control of inflow and outflow to permit repair of the injury. Unfortunately, many bowel injuries are not recognized at the time of the procedure, and nearly half are not noticed until more than 24 hours postoperatively. This obviously leads to severe sequelae and may be prevented by careful dissection and inspection at the conclusion of the procedure.

**EQUIPMENT**

The complexity of minimally invasive surgery has increased and so has the technology surrounding it. This technology is generally taken for granted; however, as surgeons who perform minimally invasive surgery, we have the obligation to understand all of the technology that surrounds our specialty. This allows the surgeon to optimize the safety, cost-effectiveness, and efficiency of these procedures.

The imaging system is composed of the following 7 components: laparoscope, light source, fiber-optic light cable, camera head, video signal processor, video cable, and monitor. This results in numerous different places where the image or picture can be compromised. Understanding the video system will allow the surgeon to do basic troubleshooting.

**Laparoscopes**

Laparoscopes come in a variety of shapes and sizes, offering several different angles of view. The standard laparoscope consists of a metal shaft 24 cm in length containing a series of quartz-rod lenses that carry the image through the length of the scope to the eyepiece. The telescope also contains parallel optical fibers that transmit light into the abdomen from the light source via a cable attached to the side of the telescope. Telescopes offer either a straight-on view at 0 degrees or can be angled at 25 to 30 or 45 to 50 degrees. The 30-degree telescope provides a total field of view of 152 degrees compared with the 0-degree telescope, which only provides a field of view of 76 degrees (Fig. 6-6).
The 30-degree telescope (A) provides a total field of view of 152 degrees compared with the 0-degree telescope (B), which provides a field of view of only 76 degrees. (© KARL STORZ SE & Co. KG, Germany.)

The most commonly used telescope has a diameter of 10 mm and provides the greatest light and visual acuity. The next most commonly used telescope is the 5-mm laparoscope, which can be placed through one of the working ports for an alternative view. Smaller diameter laparoscopes, down to a 1.1-mm scope, are available and are used mostly in children. They are not used commonly in adult patients because of an inability to direct enough light into the larger abdominal cavity. The camera is attached to the eyepiece of the laparoscope for processing.

**Light Sources**

Simply put, without light there would be no laparoscopy. High-intensity light is created with bulbs of mercury, halogen vapor, or xenon. The bulbs are available in different wattages—150 and 300 W—and should be chosen based on the type of procedure being performed. Because light is absorbed by
blood, any procedure in which bleeding is encountered may require more light. We use the stronger light sources for all advanced laparoscopy. Availability of light is a challenge in many bariatric procedures where the abdominal cavity is large. The light is carried to the fiberoptic bundles of the laparoscope via a fiberoptic cable. The current systems create even brightness across the field. It is important to mention that a lighted laparoscope or fiberoptic cable can burn through the drapes or the patient’s skin after less than 30 seconds of direct contact. This must be avoided.

**Video Camera**

A high-resolution video camera is attached to the eyepiece of the telescope and acquires the image for projection on the monitor. The video image is transmitted via a cable to a video unit, where it is processed into either an analog or a digital form. Analog is an electrical signal with a continuously varying wave or shift of intensity or frequency of voltage. Digital is a data signal with information represented by ones and zeros and is interpreted by a computer. These are the methods by which the picture is transmitted to the video monitor. The camera and cable are designed so that they can be sterilized in glutaraldehyde.

The camera iris directly controls the amount of light processed by opening the aperture of the camera. The gain controls the brightness of the image under conditions of low light by recruiting pixels to increase signal strength. Clearly, this step results in some loss of image resolution. This increases light but results in a grainy picture with poorer resolution. It also may create a loss of color accuracy owing to amplification of the noise-to-signal ratio.

Three-dimensional camera systems have been introduced for over a decade without substantial interest. These systems usually required surgeons to wear special glasses or head-up displays that allowed the integration of two image channels into a single image. Multiple authors have advocated for the use of 3-dimensional camera systems; however, limited data support the cost-effectiveness, and side effects for surgeons can occur with use, including eye strain, headache, dizziness, and disorientation. Recent advancements in technology may stimulate the rebirth of this concept. With newer systems, 3-dimensional laparoscopy appears to improve speed and decrease performance errors compared to traditional (2-dimensional) laparoscopy. In addition, the side effects from 3-dimensional laparoscopy seem to have been reduced with
newer technology. However, most studies comparing these 2 image systems were done in a simulated setting, and more clinical studies are needed.\textsuperscript{37}

**Video Monitors**

High-resolution video monitors are used to display the image. Optimal monitor size varies but ranges from 19 to 21 in. Smaller monitors may be used if placed close to the operative field. Larger monitors provide little advantage outside of a display setting. Cathode-ray monitors (analog) are being replaced rapidly by flat-panel (digital) displays with excellent color and spatial resolution. These monitors may be positioned optimally when hung from the ceiling on light booms.

**Insufflators**

An insufflator delivers gas from a high-pressure cylinder to the patient at a high rate with low and accurately controlled pressure. Some insufflators have an internal filter that prevents contamination of the insufflator with the gas from the patient’s abdomen and similarly filters any particulate matter that may be freed from the inside of an aging gas cylinder. Others require use with disposable insufflator tubing that has a filter on it. Some insufflators provide heated or humidified gas, but clinical benefit due to these theoretically desirable features has yet to be proven.

**INSTRUMENTATION**

The instruments used in laparoscopic surgery are similar to those of open surgery at the tips but are different in that they are attached to a long rod that can be placed through laparoscopic ports. Standard-length instruments possess a 30-cm-long shaft, but longer instruments (up to 45 cm in length) have been developed for bariatric surgery. The handles come in many varieties and must be chosen based on comfort and ergonomics, as well as the need for a locking or nonlocking mechanism. The shaft of most hand instruments is 5 mm wide; however, some specialized dissectors are available only in a 10-mm width. Pediatric laparoscopy instrumentation is generally 2 to 3 mm in diameter (Fig. 6-7). There are many types of bowel graspers with
different types of teeth (Fig. 6-8). The most atraumatic grasper has small, smooth teeth like a Debakey forceps. This has the advantage of not tearing the tissues and can be used on almost all organs. We use the Hunter grasper (Jarit), which, like a Debakey, can be used to grasp bowel and also can be used to grasp a needle. An additional benefit is that the tip is blunt and not prone to causing tissue trauma. Another commonly used bowel grasper is the Glassman (Storz), which is atraumatic and is slightly longer than the standard-sized Hunter grasper. It is fenestrated and cannot be used to grasp a needle. For some tissues, these instruments do not “grip” well enough, and bigger teeth or a different tip, such as those of Allis and Babcock clamps, is preferred. We reserve these larger-toothed instruments only for organs that are being removed, such as the gallbladder, or for thicker tissue, such as the stomach. The rule is to be gentle because small injuries can take a relatively long time to fix laparoscopically.
The most commonly used dissector is the Maryland dissector (Fig. 6-9). It is useful for dissecting small ductal structures such as the cystic duct and can be used when dissecting vessels. Another use for the Maryland dissector is that it can be attached to monopolar cautery and used to grasp and cauterize a bleeding vessel (this should not be done with bowel graspers). The Maryland dissector should not be used to grasp delicate tissue because too much pressure is applied over a very small area, much like erroneously using a Kelly clamp for grasping tissue. Very delicate right-angle dissectors can be used for renal, adrenal, and splenic vessels and are less traumatic than the Maryland dissector because there are no ridges.
Hemostasis

Hemostasis can be achieved using current from a monopolar electrosurgical generator applied to common instruments and controlled with a foot pedal. One of the most useful instruments for dissection is a disposable hook attached to the hand-held Bovie device for dissection (Valley Labs/Conmed and others). If a vessel has been transected and is bleeding but is too large to control with monopolar electrosurgery, a pretied lassolike suture (Endo-loop, Ethicon Endosurgery) can be helpful. Laparoscopic clips are handy for small identifiable vessels but should not be used when a vessel is not identified. The clip is only 7 mm in length and is not useful for vessels larger than this. When the vessel is not clearly identified but the bleeding site is, ultrasonic shears and some bipolar instruments such as the LigaSure device (Covidien, Mansfield, MA) can be helpful. These instruments have the advantage of facilitating dissection while providing hemostasis for larger bleeding vessels.

Monopolar Electrosurgery

Although hemostasis is obtained using the same electrosurgical generator that is used in open surgery, there are hazards that are unique to minimally invasive surgery. The most frequently used method of delivering electrosurgery is monopolar. The desired surgical effect is hemostasis, and this is obtained by production of heat. Alternating current at 50,000 Hz (household current is 60 Hz) is generated and travels through an active electrode. The active electrode can be a Bovie tip in open surgery or, in laparoscopy, an instrument that is connected to the generator by the monopolar cord. The current passes into the target tissue at sufficiently high current density to cause a great deal of heat. Depending on tissue heating, coagulation, fulguration, or vaporization of the tissue occurs. The circuit is completed by the return of the electrons broadly spread through the tissue (insufficiently dense to cause any adverse effect) back to the generator via the return electrode (grounding pad).

In open surgery, monopolar current sometimes is passed from the active electrode (Bovie tip) to the patient via another conductive instrument, the forceps. This is called direct coupling. In laparoscopy, it is not prudent to touch the active electrode (an activated instrument) on or near other conductive instruments within the abdominal cavity, that is, the laparoscope.
or other working instruments. Direct coupling in minimally invasive surgery always should be avoided because injury may occur out of the surgeon’s field of view. It is also not prudent to activate the generator in “midair” because the current may travel out of the surgeon’s field of view to a crack in the insulation of a laparoscopic instrument. This results in transfer of current to a small area that generates heat and can produce an injury. All laparoscopic instruments should be checked for cracks in the insulation before being used.

Ultrasonic Shears

Before the introduction of ultrasonic shears, larger vessels had to be tied off individually. This was very tedious laparoscopically, especially with the division of short gastric vessels during fundoplication. The development of the ultrasonic shears was revolutionary, allowing surgeons to divide larger vessels quickly and dissect simultaneously. Ultrasonic energy or sound waves are used to ablate, cauterize, and cut tissues. A generator produces a 55.5-kHz (55,500 Hz) electrical signal that travels via a cable to a piezoelectric crystal stack mounted in the transducer. The crystal stack converts the electrical signal to mechanical vibration at the same frequency. The ultrasonic vibration is amplified as it traverses the length of the titanium probe that is the active blade of the scalpel. Shearing forces separate tissue and heat the surrounding tissue, thereby coagulating and sealing blood vessels without burning. Damage to adjacent tissues is low, although the active blade can become quite hot, and burn injuries can occur.

Bipolar Electrosurgery

Bipolar electrosurgery coagulates tissue by passing a high-frequency, low-voltage electric current between 2 directly apposed electrodes. Laparoscopic general surgeons use it much less frequently because an additional maneuver must be made to divide the tissue. The LigaSure, a newer bipolar device, coagulates larger vessels (up to 7 mm in diameter) and seals tissue and has a knife available for subsequent division of the tissue between the jaws of the forceps. The instrument makes a sound when the tissue within the jaw has been coagulated safely. The advantage is that division of larger vessels can be performed safely. Unfortunately, it is relatively slow to use as a dissecting instrument, and the tip is not very useful for dissection because it is straight.
and wide. It does not produce a large amount of heat, and damage to surrounding tissues is low.

**SUTURING**

Intracorporeal suturing may be out of the realm of the fundamentals of a laparoscopic surgery chapter. However, obtaining this skill is critical for successful performance of many laparoscopic procedures. A fundamental skill of laparoscopic surgery is the ability to place a suture accurately and tie a knot with a needle holder and a standard surgical suture. This skill can be mastered easily with a training box. Various suture aids have been developed, such as the EndoStitch (USSC), and can be used as a substitute. However, these devices are expensive, and the range of suture and needle sizes and types is limited. Many surgeons believe that an extracorporeal knot is acceptable because it is easier to create a knot outside the patient and slide it down with a knot pusher. In most settings, this is not true because securing an extracorporeal knot creates “sawing” of the tissue as the suture is pulled through or around it. This often results in tissue tearing. For interrupted suturing, the sliding square knot is the simplest most secure knot to master (Fig. 6-10).
THE PHYSIOLOGIC EFFECTS OF PNEUMOPERITONEUM

The pneumoperitoneum has many effects that are only partially known despite years of study in humans and in animal models. There are effects resulting from the pressure within the abdomen and effects resulting from the composition of the gas used, generally CO₂. The effects of pneumoperitoneum can be divided into local effects and systemic effects from hypercarbia.
Local Effects

The pressure within the abdomen from pneumoperitoneum decreases venous return by collapsing the intra-abdominal veins, especially in volume-depleted patients. This decrease in venous return may lead to decreased cardiac output. To compensate, there is an elevation in the heart rate, which increases myocardial oxygen demand. High-risk cardiopulmonary patients cannot always meet the demand and may not tolerate a laparoscopic procedure. In volume-expanded healthy patients with full intra-abdominal capacitance vessels (veins), the increased intra-abdominal pressure actually may serve as a pump that increases right atrial filling pressure.

Through a different mechanism associated with catecholamine release triggered by CO₂ pneumoperitoneum, heart rate rises along with systemic vascular resistance. This may lead to hypertension and impair visceral blood flow. It is not uncommon after the induction of pneumoperitoneum for the heart rate to rise along with the mean arterial pressure. This leads to a minimal effect in a young, healthy patient; however, in elderly, compromised patient, the strain on the heart can lead to hypotension, end-organ hypoperfusion, and ST-segment changes.

To minimize the cardiovascular effects of pneumoperitoneum, it is important that patients have adequate preoperative hydration. By insufflating the abdomen slowly, the vagal response to peritoneal stretching may be diminished and vagally mediated bradycardia avoided. Additionally, if cardiovascular effects are noted during insufflation or during the maintenance of pneumoperitoneum, the insufflation pressures should be lowered from the usual 15 to 12 mm Hg, or pneumoperitoneum should be evacuated while the anesthesiologist sorts out the cardiovascular changes. Taking patients out of the steep reverse Trendelenburg position can help to increase venous return. Sometimes these effects can last for hours after desufflation.

The elevated intra-abdominal pressures restrict movement of the diaphragm, which reduces diaphragmatic excursion. This is represented as a decrease in functional residual capacity and pulmonary compliance and an increase in inspiratory pressure. Overall, there is no significant change in the physiologic dead space or shunt in patients without cardiovascular compromise. Bardoczky and colleagues studied 7 healthy patients undergoing laparoscopy with CO₂ pneumoperitoneum. After the induction of
pneumoperitoneum, peak airway and plateau airway pressures increased by 50% and 81%, respectively. Bronchopulmonary compliance decreased by 47% during the period of increased intra-abdominal pressure. After desufflation, peak and plateau pressures remained elevated by 36% and 27%, respectively, for 2 to 6 hours. Compliance remained at 86% of the preinsufflation value.

Urine output often is diminished during laparoscopic procedures and usually is the result of diminished renal blood flow owing to the cardiovascular effects of pneumoperitoneum and direct pressure on the renal veins. In addition to direct effects, elevated intra-abdominal pressure results in release of antidiuretic hormone (ADH) by the pituitary, resulting in oliguria that may last 30 to 60 minutes after the pneumoperitoneum is released. Aggressive fluid hydration during pneumoperitoneum increases urine output. Positional changes can affect the collection of urine in the Foley catheter and must be taken into consideration if anuria is noted.

**Systemic Effects**

**HYPERCAPNIA**

Hypercapnia and acidosis are seen with pneumoperitoneum and are likely due to the absorption of CO₂ from the peritoneal cavity. In the ventilated patient, increasing respiratory rate or vital capacity must compensate for these changes. At extremes, increases in tidal volume may risk barotraumas, and increases in respiratory rates diminish time for gas mixing, increasing dead-space ventilation. A first steady state in PaCO₂ is reached around 15 to 30 minutes after introduction of the pneumoperitoneum. After this period, increases in PaCO₂ suggest that existing body buffers (>90% exist in bone) have been exhausted. Sudden increases may be related to port slippage and extraperitoneal or subcutaneous diffusion of CO₂. This will resolve spontaneously once the port is repositioned.

Hypercapnia and acidosis that are difficult to control may follow, especially in elderly patients, those undergoing long operations, and patients with pulmonary insufficiency. Our response to this is to desufflate the abdomen for 10 to 15 minutes. If reinsufflation results in recurrent hypercapnia, then we change insufflation gases (see above) or convert to an
open operation. Acidosis can persist for hours after desufflation. Other complications of pneumoperitoneum that are less frequent but may be life threatening include CO₂ embolism and capnothorax.

**CARBON DIOXIDE EMBOLUS**

The incidence of clinically significant CO₂ embolism is very low, although recent reports using more sensitive tests suggest that tiny bubbles of gas are present commonly in the right side of the heart during laparoscopic procedures. Clinically important CO₂ embolism may be noted by unexplained hypotension and hypoxia during the operation. There is a characteristic millwheel murmur that can be detected with auscultation of the chest. This is produced by contraction of the right ventricle against the blood–gas interface. Usually the anesthesiologist notes an exponential decrease in the end-tidal CO₂, which is consistent with complete right ventricular outflow obstruction. The mainstays of treatment are immediate evacuation of the pneumoperitoneum and placement of the patient in the left lateral decubitus, head down (Durant) position. This allows the CO₂ bubble to “float” to the apex of the right ventricle, where it is less likely to cause right ventricular outflow tract obstruction. It is important to administer 100% oxygen and hyperventilate the patient during this period. Additionally, aspiration of gas through a central venous line may be performed.

**CAPNOTHORAX/PNEUMOTHORAX**

Capnothorax can be caused by CO₂ escaping into the chest through a defect in the diaphragm or tracking through fascial planes during dissection of the esophageal hiatus. It also can be due to opening of pleuropertitoneal ducts most commonly seen on the right side. Pleural tears during fundoplication can lead to pneumothorax, and additionally, the usual causes of pneumothorax, such as ruptured bullae, may be the etiology. The effects of CO₂ gas in the chest usually are noted as decreased O₂ saturation (a result of shunting induced by lung collapse), increased airway pressure, decreased pulmonary compliance, and increases in CO₂ and end-tidal CO₂. The treatment is to desufflate the abdomen, stop CO₂ administration, correct the hypoxemia by adjusting the ventilator, apply positive end-expiratory pressure
(PEEP), if possible, and decrease the intra-abdominal pressure as much as possible. The recommendation is to avoid thoracentesis because this usually resolves with anesthetic management. We generally evacuate the capnothorax directly at the end of the procedure with a red rubber catheter placed across the diaphragm (through the pleural defect) and brought out a trocar site. The external end of the catheter is placed under water as the lung is inflated and then removed from the water when the bubbles stop. We do not obtain chest radiographs in the recovery room after these maneuvers if there is no evidence of hypoxia on 2 L/min of O₂ flow. Patients should be maintained on supplemental oxygen to help facilitate absorption of the CO₂ from the pleural space.

SPECIAL CONSIDERATIONS

Pregnancy

There are many advantages of using laparoscopy in a pregnant patient. These include decreased fetal respiratory depression, lower risk of wound complication, and improved visualization with decreased uterine mobilization or irritation. The later may result in lower rates of spontaneous abortion and preterm delivery. Historical recommendations were to delay any surgical intervention until the second trimester; however, recent literature has shown that laparoscopic surgery can be performed safely during any trimester. Intra-abdominal access can be safely accomplished with an open (Hasson) technique, and the location of access should be adjusted according to uterine fundal height. Finally maternal and fetal monitoring should be part of any pregnant patient’s care and should continue throughout the hospitalization. Obstetric consultation should be obtained; however, it should not delay the treatment of any acute abdominal process because such delay may increase the risk of maternal and fetal morbidity and mortality.⁴⁴

CONCLUSIONS

Although minimally invasive surgery is firmly established in modern surgery, its safe performance can be ensured only with mastery of the basics. Basic
skills used in laparoscopy include evaluation of a patient based on a new set of considerations, safe use of devices for abdominal access and instrumentation, and mastery of complex manual skills and intraoperative assessment of novel physiologic parameters. Laparoscopic surgery has become the gold standard approach to several operations and will only be employed more in the future as technical innovations allow us to care for our patients in new and better ways.

REFERENCES


INTRODUCTION

Laparoscopy has evolved tremendously in the past 40 years, from a diagnostic tool to a surgical platform with nearly as many therapeutic applications as open surgery. In the most capable hands the only current primary limitation to minimally invasive approaches to most gastrointestinal (GI) cancers is the size of the incision required for removal of the specimen(s). However, it is clear that the most advanced techniques require extensive training and operative skill to perform safely and consistently on unselected patients. Given these skill sets are not realistically achievable by many surgeons, some techniques such as minimally invasive esophageal, hepatic, and pancreatic resections will remain in the purview of highly specialized practitioners. More recently, laparoscopy is being supplanted by the addition of the robotic minimally invasive platform with its promise of improved surgical exposure and increased instrument dexterity. It seems likely that with the continued advancement of technology in the field, the frontier of minimally invasive surgery will continue to expand.
While advanced laparoscopic and robotic-assisted techniques require highly specialized skill sets, diagnostic and staging laparoscopy techniques have broad clinical applicability to many GI malignancies, are easily performed, and often provide valuable information that directly impacts clinical decision making. Here we describe the use of laparoscopy in the diagnosis and treatment of common GI malignancies.

**DIAGNOSTIC/STAGING LAPAROSCOPY**

Preoperative history and physical examination are performed with particular attention to cardiopulmonary comorbidities, coagulopathy, and overall functional/nutritional reserve as with any open surgery. As laparoscopy is nearly always performed under general anesthetic and with CO\textsubscript{2} insufflation of the abdomen, there can be significant physiologic stress, particularly in patients with limited cardiopulmonary reserve. In most cases these comorbidities may be mitigated, allowing safe conduct of operation.

The patient is positioned supine, pressure points padded, and secured to the operating table. Arms may be extended or tucked according to surgeon preference and region(s) of the abdomen to be explored. After induction of anesthesia with medical paralysis, the peritoneum is accessed via either an open (Hasson) or closed (Veress or optical separator trocar) technique. Initial access is commonly at the umbilicus for Hasson and Veress techniques when there have been no prior operations, otherwise access may be gained through a paramedian incision (Fig. 7-1). Optical separators are best utilized in the left upper quadrant through the rectus muscle where adhesions are typically sparse. The authors prefer an optical trocar technique in most instances. CO\textsubscript{2} insufflation at 12 to 15 mm Hg is used except where cardiopulmonary disease prohibits full insufflation and lower pressures of 10 to 12 mm Hg may be used.
A 30-degree 5-mm scope is inserted and initial inspection commenced with attention to the presence of ascites, omental/peritoneal nodules, or liver masses. Next, additional trocars are placed in a manner that allows the region of primary interest to be examined with a head-on view and instrument ports to be aligned with the viewing angle (Fig. 7-1). The number and size of additional trocars will depend on the need for biopsies and other interventions, though a complete diagnostic laparoscopy with cup biopsies of the liver or peritoneum will generally require two additional 5-mm trocars. If peritoneal cytology is to be performed, it is done prior to manipulation or dissection of tissues by instilling 250 mL normal saline into each of the upper
quadrants and aspiration into a Lugol’s trap.

Examination of the peritoneum is performed systematically, beginning in the right upper quadrant. With the patient in reverse Trendelenberg positioning and the right side tilted upward, the right lobe of the liver is gently retracted to allow examination of the surface of the diaphragm and then elevated to view the undersurface of the liver, gallbladder, and porta hepatis (Fig. 7-2). Next, with the left side elevated, the left hemidiaphragm and left lateral segment of the liver are examined. Great care is taken not to damage the spleen with inadvertent or overly aggressive manipulation. Elevation of the left lateral segment reveals the hepatogastric ligament (Fig. 7-3), which may be opened along the pars flaccida to gain access to the lesser sac and allow biopsy of hepatic, celiac, and left gastric artery lymph nodes if indicated.

FIGURE 7-2 Laparoscopic “palpation” of the liver. Note mucinous tumor adherent to the left lobe of the liver and ligamentum teres.

With the patient in neutral positioning, the omentum is reflected upward, exposing the transverse colon, which is elevated allowing inspection of the transverse mesocolon and the ligament of Treitz—sites of potential locally advanced disease or lymphadenopathy in pancreatic cancer or lymphoma, for
example (Fig. 7-3). The small intestine may be examined from ligament of Treitz to ileocecal valve at this time as well. Finally, the patient is placed in Trendelenberg position and the small bowel and colon swept out of the pelvis to facilitate examination of the peritoneum and for females, pelvic organs (Fig. 7-4).

**FIGURE 7-3** Pars flaccida of the lesser omentum with caudate lobe visible beneath.
Laparoscopic ultrasound (LUS) may be performed to examine the liver, lymph nodes (peri-portal, celiac, peri-aortic, etc.) or other solid organs, including the pancreas, though this requires opening the gastrocolic ligament along the greater curve of the stomach to gain access to the lesser sac. Liver ultrasound in particular allows identification and core-needle biopsy of parenchymal masses not apparent on visual inspection.

Upon completion of the examination of the peritoneum, the insufflation is released and the trocars are withdrawn under direct vision, taking care to inspect for bleeding. Fascial incisions of 10 mm or more are closed to prevent herniation of abdominal contents.

LAPAROSCOPY AS A DIAGNOSTIC/STAGING TOOL

Esophageal/Gastric Malignancy

Squamous cell carcinoma and adenocarcinoma of the proximal and middle
one-third of the esophagus is associated with a lower likelihood of liver metastases and peritoneal disease, and thus diagnostic laparoscopy is seldom useful unless there is suspicion of metastatic disease or inconclusive cross-sectional imaging. For adenocarcinoma of the distal esophagus and gastroesophageal (GE) junction, the National Comprehensive Cancer Network (NCCN) guidelines currently recommend a metastatic workup including PET/CT. PET imaging aids in the detection of lymph node metastases and metastatic disease when compared with CT and endoscopic ultrasound (EUS), though its accuracy is still modest at 70% to 82%. Currently, staging laparoscopy is an optional part of the staging assessment on the basis that its role is poorly defined with some evidence for and some evidence against its routine use.

de Graff et al. performed staging laparoscopy in 416 patients with esophageal and GE junction tumors that were resectable by CT criteria. They found 84 (20.2%) patients had unresectable disease identified at laparoscopy (locally advanced in 17, lymph node disease in 14, and metastases in 63) that precluded resection. Twenty-seven patients who went on to have laparotomies had unresectable disease (metastases in 11 and locally advanced disease in 16), yielding a sensitivity of laparoscopy of 88%. As mentioned earlier, the yield of staging laparoscopy for proximal and mid-esophageal tumors and for squamous cell carcinoma was low (laparoscopy changed management in 0/28 and 1/33 cases, respectively). Neither CT/PET nor EUS was used for the preoperative staging evaluation in this study. Both have been shown to improve the ability to predict resectability and are in routine use today. As a result, the utility of routine staging laparoscopy is probably overestimated in this case.

The addition of LUS to standard staging laparoscopy has been reported by Wakelin et al. Endoscopic ultrasound was better at determining T stage except where stricture prevented complete examination. However, LUS was complementary to CT for assessment of metastatic disease. They reported an accuracy of staging laparoscopy with LUS of 81% for detection of metastatic disease compared to 72% for CT. LUS was ineffective in evaluating tumors above the diaphragm. In practice, LUS is unlikely to provide additional information except in instances where EUS is unable to be performed.

Recent studies have provided important information about the negative prognostic significance of positive peritoneal cytology, which increases the
importance of laparoscopy as a staging tool. Nath et al. evaluated 255 patients with esophageal (n = 82), GE junction (n = 48), and gastric (n = 125) cancers and no evidence of unresectability on preoperative EUS and CT (without PET). They found 48 patients (18.8%) with macroscopic metastatic disease and another 15 (5.9%) with positive cytology. Gastric cancer patients had radiographically occult metastatic peritoneal disease 28.8% of the time. The authors found no difference in survival between patients with macroscopic metastatic disease and only positive cytology (median survival 9 vs 13 months; \( p = 0.52 \)) which led them to conclude curative resection should not be performed for patients with positive peritoneal cytology.

Nearly identical findings were reported by Convie et al. with macroscopic metastases in 22.6% of gastric adenocarcinoma patients and 11.8% of esophageal carcinoma (n = 136 adenocarcinoma, 22 squamous). Cytology was positive in an additional five gastric and six esophageal carcinoma patients. The authors found positive cytology to be an equally poor prognostic sign as macroscopic metastatic disease.

Another study by Munasinghe et al. demonstrated that the location of lavage and collection of the cytology specimen is important, with the greatest yield coming from lavage and aspiration of the subphrenic region (sensitivity 90.7%), while pelvic samples have lower sensitivity (76.7%). In a study of 316 patients with esophageal, GE junction, and gastric cancers, pelvic aspiration alone understaged patients 23.3% of the time. The yield of staging laparoscopy alone was 8.9% and the addition of cytology identified another 13.6% of patients with advanced disease, for a total yield of 22.5%. Patients in this study were staged preoperatively with CT, EUS, and PET-CT providing evidence that staging laparoscopy, particularly in combination with cytology, provides meaningful information, even in the era of advanced cross-sectional imaging.

Neoadjuvant chemotherapy and chemoradiation protocols are increasingly being investigated and implemented, and though overall outcomes appear to be improved there are some patients who progress while receiving neoadjuvant therapy. The role of repeat staging laparoscopy with peritoneal cytology was investigated by Cardona et al., who found that 7% of patients had radiographically occult metastatic disease at the time of repeat laparoscopy, though cytology was only positive in the absence of macroscopic metastatic disease in one patient. They concluded that repeat
staging laparoscopy was warranted but performing cytology was not, given its low yield.\textsuperscript{12}

**Primary and Secondary Hepatobiliary Malignancy**

Preoperative imaging techniques have comparatively low sensitivity for detecting metastatic and locally invasive disease in hepatobiliary malignancies such as gallbladder carcinoma and hilar cholangiocarcinoma (HC). As an example, the sensitivity of PET/CT for unresectability of gallbladder carcinoma in one recent study was only 56\%,\textsuperscript{13} and the accuracy of predicting resectability of cholangiocarcinoma (either hilar or intrahepatic) was 72.4\% for PET/CT in another study.\textsuperscript{14} A recent expert panel consensus statement on intrahepatic cholangiocarcinoma concluded in part: “…a substantial number of unresectable patients will benefit from staging laparoscopy… [and] staging laparoscopy should be routinely utilized in high-risk patients (i.e. patients with multicentric disease, high CA 19-9, questionable vascular invasion or suspicion of peritoneal disease)…”\textsuperscript{15}

Goere et al. performed staging laparoscopy in 39 patients with gallbladder carcinoma, intrahepatic cholangiocarcinoma (IHC), and HC.\textsuperscript{16} All patients had triple-phase contrast CT and 90\% had MRI prior to staging laparoscopy. They found metastatic disease or cirrhosis precluding resection in 14 patients (36\%). Another nine patients were found to be unresectable on laparotomy, primarily because of vascular invasion or lymph node metastases. Only one patient had peritoneal metastases that were missed on laparoscopy and two patients had previously unrecognized liver metastases. The yield of laparoscopy was highest for gallbladder carcinoma (62\%, accuracy 83\%) while the yield for IHC (yield 36\%, accuracy 67\%) and HC (yield 25\%, accuracy 45\%) was somewhat lower. The authors recommended that staging laparoscopy be performed routinely for gallbladder carcinoma and IHC and selectively for HC.

Similarly, D’Angelica et al. studied the role of staging laparoscopy for both primary and secondary hepatobiliary malignancy in 401 patients and found a yield of 21\% and an accuracy of 54.9\%.\textsuperscript{17} Ninety-seven percent of study patients had preoperative CT, 45.9\% had MRI, and 86.7\% had two or more studies. The yield was highest for gallbladder carcinoma at nearly 50\% and lowest for primary hepatocellular carcinoma (<20\%) and metastatic
colorectal cancer (10%). Overall accuracy for staging laparoscopy was 54.9% with most failures due to vascular invasion or lymph node metastases. The authors also performed LUS in 168 patients, and 25 (14.9%) of these yielded additional findings not seen on laparoscopy, with 8 LUS exams primarily responsible for preventing laparotomy. Finally, the authors found morbidity and hospital length of stay were significantly less in unresectable patients who were spared a laparotomy (morbidity 9.5% vs 27.5% and hospital stay 3 days vs 9 days).

In a study by Russolillo et al., 100 patients with preoperative imaging suggesting resectable gallbladder carcinoma, HC, or borderline resectable IHC (defined as a tumor larger than 10 cm or adjacent to or infiltrating the inferior vena cava, a major hepatic vein, bile duct confluence, or a first-order Glissonian pedicle) underwent staging laparoscopy combined with LUS. The overall yield and accuracy of laparoscopy was 18% and 60%, respectively. This was increased to a yield of 24% and accuracy of 80% with the addition of LUS. In the six patients who had false negative staging laparoscopies with LUS the reason for failure was peritoneal metastases ($n = 2$), lymph node metastases ($n = 2$), or vascular invasion ($n = 2$). Of note, the only factor that predicted the failure of staging laparoscopy with LUS to identify unresectable disease was preoperative biliary drainage.

**Pancreatic Malignancy**

A recent Cochrane review reported a meta-analysis of 15 studies including 1015 patients over a period of 26 years (1986-2012) to determine the diagnostic accuracy of laparoscopy for resectability of pancreatic or perianpillary malignancy following CT scanning. They found the pretest probability of unresectable disease after CT scanning alone was 40.3% and the cumulative sensitivity of diagnostic laparoscopy was 68.7% (95% confidence interval [CI] 54.3%-80.2%). Thus the post-test probability of unresectable disease was 17%. The authors concluded that 23 laparotomies could be avoided for every 100 patients by performing laparoscopy in conjunction with CT scan. A subgroup analysis of only pancreatic cancer patients found similar results.

These data indicate that routine laparoscopy prior to planned laparotomy should be strongly considered given the fairly high likelihood of undetected
metastatic disease. However, it is important to note that over half of the patients included in the meta-analysis were from studies published 15 years or more prior to the current study. In modern practice, the advent of multidetector helical CT scans and multiphase contrast administration protocols have increased the sensitivity of cross-sectional imaging considerably, allowing for the detection of more subtle metastatic disease as well as locally advanced disease that would preclude resection. Modern CT provides a sensitivity and specificity of 85% and 82%, respectively, for vascular involvement and 88% and 89% for detection of liver metastases. As a result, diagnostic laparoscopy is not a compulsory prelude to laparotomy in many practitioners’ hands.

Staging laparoscopy may be performed on a more limited basis when the pretest probability of metastatic or locally advanced disease is high, as when the CA19-9 is markedly elevated. This was studied by Maithel et al., who found that serum CA19-9 values greater than 130 U/mL were predictive of unresectability, particularly for distal cancers. The most common site of unresectable disease was metastatic disease in the liver or peritoneum. Another more recent study found a CA19-9 value of 215.37 had a sensitivity of 72.7% and specificity of 52.3% for radiographically occult metastatic disease seen at time of laparoscopy. Of note, 5% to 10% of patients do not have the Lewis antigen required to express CA19-9 and thus will not have elevated CA19-9 values, regardless of their resectability. As a result, a low CA19-9 value should not preclude diagnostic laparoscopy if preoperative imaging is equivocal. Diagnostic laparoscopy may also provide higher yield, and should be utilized when there is a question of unresectable disease on preoperative imaging.

Some metastatic disease on the posterior surface of the liver or on the retroperitoneum abutting the duodenum may not be visible at the time of standard diagnostic laparoscopy. Schnelldorfer et al. reported a series of 274 patients who underwent either initial staging laparoscopy followed by laparotomy (if laparoscopy was negative) or initial laparotomy. Both groups had radiographically occult metastatic disease 11% of the time, though only 2% of patients were found to have metastases on laparoscopy. The remaining 9% had metastases that were identified only on laparotomy. These were found on the posterior surface of the liver, paraduodenal retroperitoneum, proximal jejunal mesentery, and in the lesser sac. The authors argued that advanced laparoscopic techniques to mobilize and expose these areas are
warranted to identify more subtle metastatic disease. More extensive laparoscopic dissection such as a Kocher maneuver and mobilization of the right lobe of the liver should be reserved for cases in which there is concern preoperatively for unresectable disease, and should only be performed by experienced laparoscopists with advanced laparoscopy capabilities.

Several studies have examined the use of LUS to evaluate the liver for subcapsular/parenchymal metastases not visible on laparoscopy as well as for vascular invasion or non-regional lymph node metastases (ie, celiac/para-aortic). Piccolboni et al. performed diagnostic laparoscopy with LUS in 18 consecutive patients, four of whom had inconclusive findings of unresectable disease on preoperative imaging. LUS identified parenchymal liver metastases in two patients and vascular involvement precluding resection in another two. The authors concluded LUS was a necessary adjunct to laparoscopy in order to determine resectability for the four patients with equivocal preoperative imaging. A larger study of 305 patients found the overall accuracy of preoperative CT for predicting resectability was 68.6%, and diagnostic laparoscopy with LUS increased this to 81%. Importantly, 4/49 patients who were deemed unresectable by CT were found to be resectable by LUS. Diagnostic laparoscopy and LUS influenced operative management 13.4% of the time.

Another study by Barabino et al. examined the role of LUS in the eras before and after the introduction of multidetector CTs. Prior to modern CT the authors performed LUS routinely and found that LUS changed the surgical strategy 30% of the time and accurately predicted resectability in 96% of patients thought to be resectable on preoperative imaging and 95% of patients who were deemed “doubtful” preoperatively. The overall yield of LUS was 45%. Following the advent of multidetector CT, the utility of LUS was curtailed significantly and the yield dropped to 1.8%. While the authors concluded LUS should not be a routine part of the workup for pancreatic cancer, they acknowledged that in certain cases of equivocal preoperative CT imaging it may be useful to prevent an unnecessary laparotomy.

The use of peritoneal cytology for the staging of pancreatic cancer has not been well defined. Positive peritoneal cytology may be found in 7% to 30% of diagnostic laparoscopies performed for known pancreatic malignancy and there may be an increased incidence of positive peritoneal cytology for distal
cancers.\textsuperscript{28,29} The clinical impact of positive peritoneal cytology is not defined, however, with some studies suggesting a higher likelihood of unresectability, limited survival, or subsequent peritoneal metastasis,\textsuperscript{30} while others show no difference in either survival or subsequent occurrence of metastases.\textsuperscript{31} At this time, conclusions cannot be made regarding the prognostic significance of positive cytology or the clinical utility of performing cytology as part of a diagnostic or staging workup.

\section*{Colorectal Carcinoma}

Laparoscopic surgery for colorectal carcinoma is well established and validated by numerous well-designed and executed randomized controlled trials (RCTs) (read below). Therefore, laparoscopic colectomy approaches standard-of-care status for practitioners who have undergone appropriate training. For those who have not, open colectomy is still indicated, and diagnostic laparoscopy may be helpful prior to planned resection. For patients who have obstructing tumors or bleeding, diagnostic laparoscopy will not change management and is not appropriate. In otherwise asymptomatic individuals it may identify carcinomatosis or liver metastases that would be best treated with neoadjuvant chemotherapy prior to an attempt at resection. Thankfully, the incidence of acute obstruction of partially- or near-obstructing tumors while receiving chemotherapy is low, making pretreatment diversion or colectomy for “impending obstruction” unnecessary for most asymptomatic individuals.\textsuperscript{32}

Modern CT scans are effective at determining the presence of liver metastases with a sensitivity of 75\% and specificity of 88\%.\textsuperscript{33} The detection of carcinomatosis by CT scanning is less exact with an overall sensitivity of 79\%, though the majority of detected lesions were 5 cm or more in this study.\textsuperscript{34} Smaller lesions are considerably less reliably detected on preoperative CT.\textsuperscript{35} We suggest diagnostic laparoscopy be considered for asymptomatic patients undergoing open colectomy in whom there is a concern for metastatic disease on preoperative CT (indeterminate liver lesion(s), ascites, possible omental/peritoneal disease) and who would be eligible for neoadjuvant chemotherapy. If neoadjuvant chemotherapy is not a consideration, management will not be changed and open resection should proceed without laparoscopy.
Disseminated Intraperitoneal Malignancy

Diagnostic laparoscopy may be performed prior to planned laparotomy for cytoreductive surgery with hyperthermic intraperitoneal chemoperfusion (CRS/HIPEC) to evaluate the extent of small bowel serosal involvement and the extent of disease overall (termed peritoneal carcinomatosis index [PCI]) (Fig. 7-5). These factors weigh heavily on the technical feasibility of performing cytoreductive surgery and the prognosis following CRS/HIPEC. While preoperative cross-sectional imaging with CT or MRI are mandatory components of the diagnostic workup, PCI has been shown to be poorly estimated by CT, particularly for smaller lesions <0.5 cm where CT sensitivity is 11%. Diagnostic laparoscopy with biopsy is also important as either a planned prelude to immediate laparotomy or as a staging tool performed independently from a therapeutic procedure. Biopsies are performed to determine tumor grade and to obtain tissue for additional pathologic examination such as immunohistochemistry when the site of primary tumor is uncertain.

**FIGURE 7-5** Peritoneal cancer index (PCI).

The role of diagnostic laparoscopy has been studied by Jayakrishnan et al., who found that laparoscopy as either an immediate prelude to laparotomy or
as a separate procedure prevented an unnecessary laparotomy in 27.7% (18/73) of cases. The reasons for aborting laparotomy were for excess PCI (>19) in 11 patients and absence of carcinomatosis in 7. Similarly, Iversen et al. found that implementing routine diagnostic laparoscopy to evaluate extent of disease spared 18 of 45 (40%) patients from a nontherapeutic laparotomy.

MINIMALLY INVASIVE SURGERY AS A THERAPEUTIC TOOL FOR CANCER

As noted earlier, there are myriad applications of laparoscopy as a therapeutic modality for treatment of abdominal malignancies. While it is beyond the scope of this chapter to describe the minimally invasive approaches for each, we aim to highlight the indications and outcomes here. Many of these techniques remain formidable challenges to incorporate into a practice of unselected patients, even for experienced laparoscopists. As a result, all of the data presented subsequently is subject to the caveat that acceptable perioperative and long-term oncologic outcomes for laparoscopic cancer operations are dependent on the experience of the surgeon, and many of these procedures should only be performed by surgeons with advanced training in minimally invasive surgery.

Esophagectomy/Gastrectomy

Minimally invasive esophagectomy (MIE) has been studied extensively with retrospective and nonrandomized prospective studies but only one randomized controlled trial. This study examined short-term outcomes and found significantly decreased pulmonary complications at 2 weeks and while in-hospital (34% for open and 12% for MIE). Secondary outcomes included hospital length of stay, estimated blood loss, short-term quality of life, postoperative pain, and vocal cord paralysis, all of which were decreased in the MIE group. From an oncologic standpoint there was a trend toward more margin-negative (R0) resections in the MIE group (84% vs 92%, \( p = 0.080 \)), and number of lymph nodes sampled was similar between the two groups. MIE was associated with longer operative times (329 min vs 299 min; \( p = 0.002 \)). Analysis of long-term outcomes and survival has been performed by
meta-analyses showing equivalent survival between the two techniques at 30 days and 1, 2, 3, and 5 years. However, meta-analyses have been hampered by significant heterogeneity of the studies due to many differences in perioperative management as well as multiple techniques for both open and MIE that are reported.

Laparoscopic or robotic-assisted minimally invasive gastrectomy for gastric cancer has also been reported extensively in the literature with retrospective studies but few RCTs. A recent meta-analysis of studies comparing short-term outcomes for laparoscopic distal gastrectomy (LDG) with open distal gastrectomy (ODG) included 6 RCTs and 19 observational studies (n = 3055 patients) and found that LDG was associated with similar perioperative mortality and major surgical complications but decreased overall complications, medical complications, minor surgical complications, estimated blood loss, and hospital length of stay. Operative time was longer and lymph node retrieval was less for LDG. The authors did note that the majority of the studies were performed in Eastern centers with primarily early-stage cancers, which may limit the generalizability to Western centers with higher body mass index (BMI) patients and more locally advanced disease.

Long-term outcomes for laparoscopic gastrectomy have also been analyzed by meta-analysis. Chen et al. evaluated 23 studies with 7336 patients and found that 5-year overall survival, recurrence, and cancer-related death were similar between laparoscopic and open approaches. However, given the retrospective nature of the studies included and variability in study design, there was significant confounding in the comparability of the groups as well as for extent of lymphadenectomy. At this time, in the absence of rigorous RCT data, there does not appear to be any evidence for poorer long-term outcomes associated with the laparoscopic approach. Short-term outcomes appear to be slightly better in terms of hospital stay, postoperative pain, blood loss, and minor complications.

Data evaluating the short-term and long-term outcomes of total gastrectomy are also lacking, with only nonrandomized, retrospective data at this time. As with LDG, total gastrectomy appears to be safe with comparable long-term oncologic outcomes when performed by experienced surgeons.

Palliation of obstructing distal gastric cancers may be performed by...
laparoscopic gastrojejunostomy and has been reported by Choi and others. The laparoscopic approach to palliative gastrojejunostomy is generally associated with faster return to oral intake (2.9 days vs 4.7 days). It is theorized that reduced incision size could also allow faster initiation of chemotherapy postoperatively, though this has not been studied in a comparative fashion.

Liver/Biliary Resection

Laparoscopic liver surgery is a formidable challenge and continues to grow and evolve as new techniques are developed and new technology emerges. Issues regarding minimally invasive liver and biliary surgery have been addressed in a recent consensus conference. Multiple retrospective comparison studies have been performed as well as some prospective, nonrandomized studies, but no RCTs to date have compared outcomes between open and laparoscopic techniques. Meta-analyses compiling data from studies comparing laparoscopic to open hepatectomy for malignancy have shown decreased operative blood loss and hospital length of stay, with similar rates of postoperative complications and oncologic outcomes. Morise et al. also found consistently lower rates of postoperative ascites and liver failure in patients with hepatocellular carcinoma and concomitant chronic liver disease who underwent laparoscopic hepatectomy. Laparoscopic hepatectomy for metastatic colorectal cancer (mCRC) was associated with less blood loss, transfusions, and hospital length of stay with similar operative times and equivalent disease-free and overall survival at 1, 3, and 5 years when compared to open resection in a recent meta-analysis by Schiffman et al.

Robotic-assisted hepatectomy has been retrospectively compared to laparoscopic resection and found to be equivalent in terms of perioperative outcomes including operative blood loss, negative margin rate, complication rate, 30- and 90-day mortality, and hospital length of stay. There is a significantly longer operative time associated with robotic resections, though a greater number of resections were able to be completed in a totally minimally invasive fashion with the robotic platform (93% vs 49.1%).
Pancreatectomy

As with hepatectomy, laparoscopic major pancreatectomy is a challenging undertaking. The laparoscopic pancreaticoduodenectomy (PD) is considered by some to be the Mt. Everest of minimally invasive surgery. Only a handful of highly skilled laparoscopic surgeons are able to consistently perform the operation with acceptable morbidity, mortality, conversion rates, and oncologic outcomes. Kendrick et al. reported their series of 108 laparoscopic PD versus 214 open PD and found significantly decreased hospital length of stay (6 days vs 9 days; p<0.001) and similar rates of perioperative morbidity, including pancreatic fistula. Progression-free survival was significantly longer in the laparoscopic group but overall survival was similar. The authors noted a significantly larger proportion of patients did not receive adjuvant chemotherapy within 90 days in the open group, perhaps explaining the more rapid cancer progression (12% vs 5%).

Robotic-assisted pancreatic surgery has emerged as a powerful platform to perform complex operations minimally invasively. The report of 250 procedures published by Zureikat et al. illustrates the variety of applications that are well suited to the robotic platform (Table 7-1). In their experience, the incidence of Clavien grade 3 and 4 complications (14%, 6%, respectively), International Study Group on Pancreatic Fistula (ISGPF) grade C pancreatic fistula (4%), and 30- and 90-day mortality (0.8%, 2%, respectively) all approximated or improved upon published norms. Although overall operative times were long (mean 529 min for PD) they decreased steadily throughout the study period, and in the last 50 PD cases of the series the median operative time was 360 minutes.

TABLE 7-1: SHORT-TERM OUTCOMES FOR ROBOTIC-ASSISTED PANCREATECTOMIES
In comparison to laparoscopic PD, laparoscopic distal pancreatectomy has been adopted relatively broadly and has been shown to be safe, with similar rates of operative and perioperative complications, including pancreatic fistula and less operative blood loss, earlier time to oral intake, and decreased hospital length of stay compared to open distal pancreatectomy. Oncologic outcomes are not as well studied, though a single-institution report of laparoscopic \( n = 131 \), robotic \( n = 37 \), and open \( n = 637 \) distal pancreatectomies found similar margin-negative resection rates for the three groups, though there were fewer lymph nodes harvested with the laparoscopic technique \( 15.4 \) vs \( 10.4 \) vs \( 12 \) for LDP, ODP, RDP; \( p = 0.04 \). In another single-institution, retrospective study Fernández-Cruz et al. found the median survival for patients undergoing LDP for adenocarcinoma was 14 months with adjuvant 5-FU. Although there was no comparison group, the authors commented that this approximates the survival of patients undergoing ODP for pancreatic cancer. The robotic platform may offer some advantages over the laparoscopic platform, especially when applied for pancreatic cancer.

Palliative procedures for periampullary malignancy are not as common in the current era of endoluminal duodenal stents and percutaneous or endoscopic biliary stents. There remain, however, indications for surgical bypass of either enteric obstruction, biliary obstruction, or both, such as failure of endoscopic methods. Furthermore, surgical means of palliation tend to be more durable and require less subsequent intervention or hospitalization, which is an important consideration given that advances in chemotherapeutics may help patients with unresectable disease to live longer. Laparoscopic methods for biliary and enteric (laparoscopic gastrojejunostomy [GJ]) bypass have been described and compared to both
open bypass and endoscopic bypass methods. Generally, endoscopic means of palliation are preferred to surgical methods (both open and laparoscopic) due to increased complications and hospitalization time associated with surgical procedures. Laparoscopic bypass may be considered for patients in whom endoscopic means are impossible (ie, biliary obstruction with prior Roux-en-Y) or if impending obstruction is found at the time of diagnostic/staging laparoscopy, though this should be rare in the era of high-quality cross-sectional imaging.

**Colon/Rectal Resection**

Laparoscopic colectomy is perhaps the most well-studied laparoscopic cancer operation. High-quality data including multiple RCTs and meta-analyses have validated laparoscopic colectomy as a safe and effective treatment for colon cancer. In one meta-analysis of 12 RCTs, laparoscopic colectomy was associated with lower operative blood loss, decreased postoperative pain, faster return of bowel function and resumption of oral diet postoperatively, and shorter hospital length of stay (Table 7-2). Morbidity and mortality were similar, as were cancer-related outcomes of overall survival and disease-free survival.

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<th>TABLE 7-2: SHORT-TERM OUTCOMES OF LAPAROSCOPIC COLECTOMY</th>
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<td><strong>ORT (min)</strong></td>
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*Statistically significant.
Abbreviations: LS, laparoscopic surgery; OS, open surgery; ORT, operating room time; EBL, estimated blood loss; LN, lymph node; POD, postoperative day.

It should be noted that recently some investigators have questioned the purported safety of laparoscopic colectomy and proctectomy. Sammour et al.
performed a meta-analysis of RCTs and found that for colorectal cancer operations, the laparoscopic approach was associated with an increased risk of intraoperative complications (OR 1.55, \( p = 0.009 \)) and bowel injury (OR 2.28, \( p = 0.006 \)). There were no differences noted for hemorrhage or solid organ injury.\(^{66}\) These data highlight the importance of the need for experienced surgeons with advanced laparoscopy skills.

Robotic-assisted proctectomy has become a common approach to rectal cancer and has been reported extensively in the literature, though randomized studies are lacking. A meta-analysis of seven retrospective and nonrandomized case-control studies comparing laparoscopic and robotic-assisted proctectomy found a decrease in the rate of conversion to open operation for robotic-assisted surgeries but similar outcomes in terms of blood loss, hospital stay, and pathologic variables.\(^{67}\)

Palliative procedures for obstructing colorectal carcinoma have been described\(^{68}\) and can be performed as safely as open operations in the hands of experienced laparoscopists. The main challenges involve limited “working space” due to varying degrees of small bowel and/or colonic dilation that result from the obstruction. For patients who are receiving chemotherapy, simple proximal diverting loop colostomy for an obstructing rectosigmoid cancer can be sufficient and avoid the potential morbidity associated with formal resection. Obstructing right-sided lesions can be associated with a closed-loop obstruction if the ileocecal valve is competent, and this situation is usually best managed with a formal resection with reanastomosis. Transverse colon lesions may be approached with either loop colostomy or resection, depending on patient condition and feasibility of resection.

Mucinous ascites resulting from end-stage disseminated colorectal carcinoma is a dreadful condition which is difficult palliate. Due to the viscosity of the mucin, it is not amenable to paracentesis or percutaneous drain placement, and medical therapies such as diuretics do not address the issue either (Fig. 7-6). Some have advocated laparoscopic-assisted evacuation of mucinous ascites as a method to provide relief.\(^ {69}\) Morbidity is low and the procedure can be safely repeated as necessary, given the mucin will reaccumulate over time.
CONCLUSIONS

Minimally invasive surgery is a valuable tool in the armamentarium of the cancer surgeon. As a staging and diagnostic tool it is complementary to cross-sectional imaging, and when applied rationally it provides valuable information while minimizing morbidity for cancer patients, where quality of life and the time lag to chemotherapy are very real concerns. Therapeutic uses of laparoscopy and robotic-assisted surgery for cancer operations continue to grow and evolve; the valid concerns regarding minimally invasive techniques for oncologic procedures have been addressed by several RCTs (ie, esophagectomy, colectomy). The sum total of the literature to date does not support worse oncologic outcomes for minimally invasive cancer surgery. In fact, it is likely that surgical approaches to local control of GI malignancies will be less important than improvements in systemic therapy in terms of overall survival, as has been the case in the treatment of breast cancer. At the same time, improved patient-centered outcomes seen with minimally invasive techniques have the potential to translate to better tolerance of—and increased rates of administration—for life-prolonging
adjuvant chemotherapy. Despite these advances reported in the literature, it remains essential that individual practitioners attempting these complex procedures obtain necessary training and a level of laparoscopic skill that allows for safety and maintenance of oncologic principles.

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INTRODUCTION

Innovations in robotic technology are transforming the way surgeons operate in the 21st century. Robotic surgical platforms grant surgeons access to modern-world defining robotic engineering and computer programming, which enhance the surgeon’s operative view and augment his or her manual dexterity.\(^1\)\(^-\)\(^3\) These surgical tools were developed with the goal of helping surgeons overcome the limitations of laparoscopy and to facilitate the broader adaptation of minimally invasive surgery to include more complex abdominal procedures.\(^4\)\(^-\)\(^8\) The technologic superiority of robotic surgical platforms over existing open and laparoscopic instruments is undisputed, with the potential to harvest significant advantages for the surgeon and, ultimately, translate them for improved patient outcomes.

As with all new technology, however, robotic surgery poses novel challenges for general surgeons as we begin to define its role in our clinical
practices, discern its optimal application for our patients, and determine its benefits and disadvantages. Familiarity with robotic surgical systems, the current uses, its optimum utilization, and potential future applications can facilitate the employment of the robotic surgical platforms for gastrointestinal procedures. In this chapter, we will cover the development of the robotic surgical technology and the inherent advantages of the da Vinci Surgical Systems (Intuitive Surgical, Sunnyvale, CA). The chapter will explore how surgeons can exploit specific technologic innovations of the da Vinci robotic surgical platforms in robotic Heller myotomy with fundoplication, radical gastrectomy with lymphadenectomy, and robotic colorectal resections with total mesorectal excision. We will review the results of existing studies focusing on the clinical outcomes of these select robotic gastrointestinal surgeries alone and in comparison to open and laparoscopic approaches. Finally, the chapter will highlight a few distinct features of robotic surgery and possible future applications.

**EVOLUTION OF THE ROBOTIC SURGICAL SYSTEMS**

**Development of Robotic Surgical Technology**

Robotic surgery is the utilization of specifically designed robotic surgical platforms to perform minimally invasive surgical procedures. The foundation of the robotic surgical technology is derived from the innovations of a military project endorsed by the National Aeronautics and Space Administration (NASA). The Defense Advanced Research Project Administration (DARPA) funded the research project in the 1970s. At the time, the aim of the surgical robotics project was to enable telesurgery—to create a robot that could be manipulated to care for astronauts in space aircrafts and soldiers in the battlefield without the physical presence of a surgeon alongside the patient. In 2002, the first robot-assisted telesurgery on a human, a cholecystectomy, was performed using the ZEUS system (Computer Motion, Goleta, CA). The surgeon, Dr. Jacques Marescaux, was seated at the “surgeon-side” subsystems located in New York City with a “patient-side” robot with the patient in Strasbourg, France.
Although the Zeus Robotic Surgical System is no longer used, several companies continued to develop surgical robotics; and currently, all robotic gastrointestinal operations are performed with the da Vinci Surgical Systems.\textsuperscript{14-17} They are the only robotic platforms available for abdominal surgery in the adult and pediatric populations. Since the Food and Drug Administration approved Intuitive Surgical’s da Vinci S System in the year 2000, 3 generations of da Vinci Surgical Systems, each with increasingly more sophisticated features, have been developed: the S System (2003), the Si System (2009), and the Xi System (2014).

\textbf{da Vinci Surgical Systems}

The da Vinci Surgical Systems are composed of the surgeon console and the patient-side cart. Similar to laparoscopic surgery, trocars are used as smaller incisional points of entry into the peritoneal cavity. The trocars and the surgical instruments, including the camera, are then attached to robotic arms, which are a part of the patient-side cart. Unlike both open and laparoscopic operations, the primary surgeon is not at the patient’s side but controls the operation from a distance. The surgeon operates seated at the console controlling the instruments attached to the patient-side cart (\textit{Fig. 8-1}).
Once seated at the console with the head rested on the viewing piece, the surgeon gains complete control of the robot arms with the ability to manipulate the 4 inserted instruments. Bilateral hand and foot controls require the surgeon to coordinate both hand and feet movements throughout the robotic procedure to manipulate the camera position, focus, distance, and angle along with 3 other instruments. A surgeon, resident, or a physician’s assistant with varying degrees of training, experience, and robotic and laparoscopic expertise should assist the primary surgeon at the patient bedside to exchange the instruments, clean the camera lens, help suction, and create exposure of the operative field when necessary during the procedure (Fig. 8-2). The more complex the operation and the less experienced the primary surgeon, the more experienced the bedside assistant should be.
Enhanced Robotic Features

The robotic surgical platforms possess several key innovations (Table 8-1).\textsuperscript{5,12} Predominantly, the advancements of robotic surgical platforms over the conventional laparoscopic instruments are its uniquely engineered attributes. These robotic features include the 3-dimensional (3D) high-definition camera with up to 10× magnification of the surgical anatomy. The surgeon has complete control of the camera for timely adjustments of the operative view either during a pause or simultaneously with active maneuvering of 2 other robotic arms. In addition, the scaling of motion and filtering of the surgeon’s tremor allow for increased precision and accuracy of movements unaffected by the fulcrum effect or human fatigue.
The EndoWrist (Intuitive Surgical) function providing 7 degrees of articulation is another significant technologic improvement of robotic surgery over the existing laparoscopic instruments. The ability to articulate beyond the human wrist, which only has 3 degrees of freedom during cutting, sealing, and dissecting, exists in all robotic instruments except in the robotic camera, the Harmonic Ultrasound Shears, and the stapler. Moreover, the surgeon has control of 4 arms of the robotic platform.

Several additional robotic features are available to aide in intraoperative decision making. Tilepro (Intuitive Surgical) is a multidisplay imaging program that allows for simultaneous viewing of other images (intraoperative ultrasound and endoscopies and preoperative radiologic images) that can be activated any time during the operation. In addition, the robotic camera has near-infrared optical capabilities, which allow the surgeon to see fluorescent light for delineation of surgical anatomy including lymph nodes, lymphatic drainage, blood vessels, and the entire biliary tree.

**CURRENT APPLICATION OF ROBOTIC SURGERY IN GASTROINTESTINAL DISEASES**

While the initial robotic system was intended for cardiac surgical procedures, the use of the robotic surgical platforms has been used in most surgical subspecialties including urologic, gynecologic, thoracic, vascular, transplant,
and general surgeries. In addition, until recently, the field of robotic surgery was dominated by robotic prostatectomies and benign and malignant gynecologic procedures. However, with the availability of additional features and greater number of instruments better suited for general surgery on each new robotic surgical platform (Si System and the Xi System), general surgeons are performing numerous complex robotic operations. 

Surgeons in the United States and around the world have performed a wide range of general surgical procedures with robotic assistance (Table 8-2). The robotic general surgical procedures reported to treat diseases in the foregut include Heller myotomies, hiatal hernias, antireflux surgeries (eg, Nissen fundoplication, partial fundoplications), bariatric surgery (eg, Roux-en-Y gastric bypass, sleeves), splenectomies, gastrectomies (eg, radical subtotal distal, total, or proximal gastrectomies), and lymph node dissections. For hindgut diseases, surgeons have used robotic assistance in performing simple right and left colectomies and more complex rectal resections (low anterior resection and abdominoperineal resections) with total mesorectal excisions.

**TABLE 8-2: ROBOTIC ABDOMINAL OPERATIONS**

**Foregut/Upper Abdominal Operations**
- Heller myotomy
- Antireflux surgery
- Bariatric surgery (Roux-en-Y gastric bypass, sleeves)
- Radical gastrectomy (subtotal distal, total, D2 lymphadenectomy)
- Splenectomy

**Hepatopancreaticobiliary Operations**
- Liver resection
- Pancreatic resections (pancreaticoduodenectomy, central and distal pancreatectomy, portal vein reconstruction)
- Cholecystectomy (simple, radical)

**Colorectal Operations**
- Right colectomy
- Left colectomy
Combined operations, such as colectomies with hepatectomies for metastatic colon cancer and gastrectomies with cholecystectomies for biliary disease and obesity or gastric cancer, have also been reported. Experienced surgeons are performing an increasing number of other more complex hepatopancreaticobiliary operations including liver resections, pancreatic resections (proximal, central, and distal pancreatectomies), and pancreatic resections with venous reconstructions. As pioneering surgeons explore and demonstrate the safety and feasibility of numerous robotic procedures for gastrointestinal diseases, the minimally invasive benefits of robotic surgery as an alternative to laparoscopy are quickly being revealed under critical evaluation.

**Rationale for the Robotic Approach**

**BENEFITS OF MINIMALLY INVASIVE SURGERY**

Since the first use of laparoscopy in 1982 for an “endoscopic” appendectomy, 28 minimally invasive surgery has earned a prominent place in the armamentarium of general surgeons and has proven its effectiveness in conferring clinical benefit to our patients. For years, pioneering surgeons who used this revolutionary method of operating in the abdomen through small incisions with long stick-like instruments while watching a 2-dimensional view of the operative anatomy experienced significant controversy and criticism regarding its safety, feasibility, increased cost, increased complication rates, and unknown long-term outcomes. 29 With increasing surgeon experience, large retrospective studies and well-designed prospective clinical trials have clearly defined the benefits of minimally invasive surgery for patients undergoing abdominal operations for both benign and malignant gastrointestinal diseases. 30-34
The short-term benefits attributed to the decreased trauma of a minimally invasive procedures include shorter hospital stays, less blood loss, decreased pain, earlier return to daily activities, and smaller scars. Further support for minimally invasive surgery comes from comparable long-term oncologic outcomes of cancer patients treated with laparoscopic surgery versus open operations. The conclusion of the studies is that if surgeons adhere to oncologic principles during laparoscopic surgery as they do through the open approach, patients gain the benefits of the short-term postoperative outcomes without compromising the long-term oncologic outcome.

The laparoscopic approach to abdominal operations to treat certain benign diseases such as cholecystectomy, reflux surgery, and morbid obesity has become standard of care with relatively quick adaptation periods. Unfortunately, despite studies to demonstrate improved outcome of minimally invasive surgery, in more complex abdominal operations, the widespread utilization of laparoscopy remains limited. In fact, only 10% of gastric cancer and 15% to 20% of colon cancer operations are performed minimally invasively (laparoscopically) in the United States. The limitations of laparoscopic instrumentation and the steep learning curve of the advanced laparoscopic skills are barriers to widespread use of the laparoscopic approach to complex abdominal operations.

CHALLENGES OF LAPAROSCOPY

Several formidable impediments to the broader adaptation and greater application of laparoscopy for abdominal operations exist and hinder surgeons from providing the well-accepted benefits of minimally invasive surgery to our patients. Especially for complex gastrointestinal operations, not only is substantial training required to learn the laparoscopic techniques, but also surgeons must gain high-volume experience to master the laparoscopic approach for any specific procedure. This steeper learning curve translates into longer laparoscopic operative times when compared to the open operations. In addition, experienced laparoscopic surgeons have suffered from the long-term detrimental effects of the poor ergonomics of laparoscopic instruments. Robotic surgery offers surgeons access to new technology to overcome these limitations and overcome the disadvantages of laparoscopy.
ADVANTAGES OF ROBOTIC SURGICAL SYSTEMS

Enhanced robotic features may offer the surgeon several advantages to overcome the difficulty of applying minimally invasive techniques during these complex gastrointestinal procedures. The entire procedure is performed with a 3D view of the operative field, which provides depth perception more closely resembling an open operation as opposed to the 2-dimensional flat view of the laparoscopic screens. More importantly, the 3D view is magnified and can be angled 30 degrees in several directions to see points of the operative field not readily observed during an open operation.

At all points during the operation, the surgeon has control of the camera. This allows the surgeon the ability to manipulate the camera to any position he or she wants at the exact time he or she needs. In addition, when the camera is not being repositioned, it remains steady without any unwanted movements since the robotic arm holding the camera does not fatigue as a human assistant would. This permits a well-coordinated steady 3D magnified operative view throughout the entire surgical procedure.

In fact, the surgeon controls 3 other robotic arms as well. Although only 2 instruments can be manipulated at the same time, a feature to shift control between 2 arms allows the surgeon to position 1 of the arms for retraction and helps improve exposure prior to dissection of a certain area. For example, this feature can be optimized during the suprapancreatic portion of the D2 lymph node dissection during a radical gastrectomy for locally advanced gastric cancer. The third robotic arm holding a Cadiere forceps gently retracts the pancreas in the caudal direction to expose the celiac axis and splenic artery. The exposure is maintained while the other 2 other arms holding operative instruments carry out that portion of the procedure by dissecting, cutting, burning, ligating, clipping, and providing additional retraction.\textsuperscript{51,52}

One of the major advantages of the robotic EndoWrist capability is dissection or suturing in narrow operative fields such as working in a male pelvis during robotic total mesorectal excision.\textsuperscript{26,53,54} The robotic arms have been found to be facile in the narrow pelvis where open surgery is a challenge and where laparoscopic rectal or perirectal dissection is difficult to perform. Both the EndoWrist instruments and the tremor filter in this area have been noted to be of utility around nerve-sparing procedures of the total mesorectal excision\textsuperscript{55} and during the precise cutting of the esophageal muscles in a Heller myotomy.\textsuperscript{56,57} In addition, the Large Needle Driver and
the Mega Suture Needle Driver are EndoWristed with 7 degrees of articulation providing natural turning of the suture at many angles, which facilitates quicker and more precise suturing of bowel or vessels during these gastrointestinal operations.

Among the many robotic surgical procedures already performed, the gastrointestinal procedures during which the surgeon can maximize the robotic technology for both the patient and the surgeon benefit can be exemplified in representative operations such as the robotic Heller myotomy with fundoplication, robotic radical gastrectomy with D2 lymphadenectomy, and robot-assisted colorectal resection with total mesorectal excision. As general surgeons continue to gain more experience with the robotic approach, we are affectively harvesting the novel technology afforded by the robotic surgical platforms for the surgeon benefit with the potential to translate them into improved patient outcomes.

RESULTS OF CLINICAL STUDIES

In general, surgeons can perform complex operations with increasing ease and precision with the use of the robotic surgical systems over conventional laparoscopy. Current studies of robotic operations for gastrointestinal diseases demonstrate the robotic approach to be safe and feasible and to provide our patients the benefits of minimally invasive surgery with improved outcomes compared to open operations (Table 8-3). Moreover, robotic surgeons uniformly report the use of robotic surgical systems to enhance the operative experience and confer an operative advantage during abdominal operations over laparoscopic approaches. Although, robotic surgery has not yet demonstrated any substantial improvement in clinical outcomes when compared to laparoscopy in general, with improved understanding of the superior robotic technology, surgeons have begun to harvest its advantages for specific operations.

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<th>TABLE 8-3: ADVANTAGES AND DISADVANTAGES OF ROBOTIC SURGERY COMPARED TO OPEN AND LAPAROSCOPIC APPROACH</th>
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<td><strong>Robotic Advantage Over Open Surgery</strong></td>
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<td>1. Smaller incisions</td>
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2. Less blood loss
3. Shorter hospital stay
4. Decreased pain
5. Decreased surgical site infections
6. Decreased systemic complications
7. Decreased incisional hernia rates
8. Earlier return to daily activities
9. Improved cosmetic outcome

**Robotic Advantage Over Laparoscopy**

*For the surgeon*
1. 3-Dimensional magnified high-definition view
2. Control of 4 arms
3. Improved ergonomics
4. Shorter learning curve
5. Improved accuracy and precision of dissection

*For the patient*
1. Less intraoperative blood loss
2. Improved procedure-specific short-term outcomes
   a. Heller myotomy—lower esophageal perforation
   b. Radical gastrectomy—lower learning curve
   c. Total mesorectal excision—lower conversion rate

**Disadvantages of Robotic Surgery**
1. Longer operative time
2. Additional training
3. Higher cost

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**Heller Myotomy for Achalasia: Improved Precision During Myotomy**

Robotic surgical platform allows for precise dissection of esophageal muscle layers during robotic Heller myotomy, providing an opportunity for surgeons to gain improved surgical outcomes for patients being treated for achalasia. The laparoscopic approach to Heller myotomy has become the standard.
treatment for achalasia since the minimally invasive approach demonstrated improved outcomes when compared to the open Heller myotomies. The esophageal perforation rate for laparoscopic Heller myotomy, however, remains 5% to 10%, leaving room for significant improvement. The technically challenging portion of this procedure is the requirement for precise dissection and cutting of the esophageal muscle layers without damage to the underlying esophageal mucosa. Surgeons have achieved a 0% esophageal perforation rate using the robotic surgical platforms.

The initial report of a successful robotic-assisted Heller myotomy published in 2001 by Melvin et al has been followed by several series and comparative studies. Talamini et al reported the safety and feasibility of robotic gastrointestinal procedures in 2002 including 5 successfully performed Heller myotomies. In a series of 104 patients undergoing robot-assisted Heller myotomy (RAHM), Melvin et al reported a 0% esophageal perforation rate with an improvement in the average operative time from 162.63 minutes to 113.50 minutes over a 2-year period. A multi-institutional retrospective study involving 3 institutions comparing 59 RAHM with 62 laparoscopic Heller myotomy patients resulted in similar statistically significant differences in esophageal perforation rates of 0% and 16%, respectively. This group also found that although the initial robotic operations had longer operative times, the average operative times of the last 30 robotic cases did not differ significantly from the laparoscopic approach. The surgeons attribute the improved outcome to the enhanced robotic visualization of muscular layers and improved control of the robotic instruments.

Robotic Surgery for Gastric Cancer: Shorter Learning Curve for Robotic D2 Lymphadenectomy

Minimally invasive gastric cancer operations provide significantly improved short-term patient outcomes without compromising the long-term effectiveness of properly performed radical gastrectomy with lymphadenectomy when compared to the traditional open surgery. Unfortunately, the technical difficulty of performing an extended lymphadenectomy, recommended for all surgically resectable patients with
stage II or greater gastric cancer, is well recognized. Even in open radical
gastrectomies for gastric cancer, performing D2 lymphadenectomy (removal
of all soft tissue containing the lymph nodes that drain the stomach) requires
fine dissection around the hepatoduodenal ligament and the celiac axis and
along the splenic vessels and is known to have high morbidity and mortality
rates in previously published Western studies.\textsuperscript{76,77} For laparoscopic approach
to this procedure, experienced gastric cancer surgeons report the learning
curve plateau to be over 50 cases.\textsuperscript{78-81} This is a major challenge because the
incidence of gastric cancer in the United States is low, with only a few
experienced surgeons able to offer the minimally invasive approach to their
gastric cancer patients.\textsuperscript{82}

With the advent of robot-assisted gastric cancer operations, there is a real
potential for increasing the percentage of minimally invasive surgeries
performed for gastric cancer. The advantages of the robotic surgical platform
for gastric cancer operations are several. First, in order to perform a proper
minimally invasive D2 lymphadenectomy, the procedure requires 5 ports and
2 skilled assistants, one to drive the camera and other to retract, expose, and
suction. With the robotic surgical platform, the surgeon has control of 4 of
these 5 arms, providing a steady and readily manipulated camera for the
optimum operative view at all times, the ability to create your own retraction,
and exposure with the third arm while operating with 2 arms with instruments
that have the capacity to articulate around vessels and other tissues.

Second, the robotic camera offers a superior view of the surgical anatomy,
and the enhanced dexterity provides the surgeon great assistance during the
D2 lymphadenectomy, which requires precise dissection along the pancreas
and major vessels including the anterior superior pancreaticoduodenal vein
on the head of the pancreas, hepatic artery, portal vein, common hepatic
artery, celiac artery, left gastric artery, splenic artery and vein, and at times
splenic hilum (lymph node station #10 during total gastrectomies).\textsuperscript{83,84}
Robotic gastric cancer surgeons have emphasized the importance of these
perceived superiorities of the robotic technology in helping them perform
better operations.

Robotic surgery for gastric cancer was first reported by Hashizume in
Japan (2002)\textsuperscript{85} and then by Giulianetti in the United States (2003)\textsuperscript{15} and has
since been adopted by many experienced surgeons to perform radical
gastrectomies with D2 lymphadenectomies (Table 8-4).\textsuperscript{86-90} The single-
institution safety and feasibility studies were quickly followed by comparative studies, which demonstrated the robotic surgical advantages of minimally invasive surgery in gastric cancer patients (Table 8-5). \(^{91-100}\) To date, most of the studies evaluating robotic surgery in the United States include a small number of cases, with the largest study composed of 98 patients who underwent robotic distal (n = 59), total (n = 38), or proximal (n = 1) gastrectomies over a 10-year period by Giulianotti’s group. With an average follow-up of over 3 years, the study demonstrated comparative long-term oncologic outcome to laparoscopic and open operations. The 5-year cumulative survival rates for patients with stage IA, IB, II, and III disease were 100%, 84.6%, 76.9%, and 21.5%, respectively. \(^{101}\)

### TABLE 8-4: SINGLE-INSTITUTION RETROSPECTIVE EVALUATIONS OF SHORT-TERM OUTCOME OF ROBOTIC GASTRECTOMY FOR GASTRIC CANCER

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>No. of Patients</th>
<th>OT (min)</th>
<th>EBL (mL)</th>
<th>LNs (No.)</th>
<th>Positive Margins</th>
<th>LOS (days)</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson (^{96})</td>
<td>United States</td>
<td>2007</td>
<td>7</td>
<td>420</td>
<td>300</td>
<td>24</td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Patrini (^{97})</td>
<td>Italy</td>
<td>2007</td>
<td>13</td>
<td>286</td>
<td>103</td>
<td>28</td>
<td>0</td>
<td>11</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Song (^{98})</td>
<td>Korea</td>
<td>2009</td>
<td>100</td>
<td>175</td>
<td>128</td>
<td>37</td>
<td>0</td>
<td>8</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>D’Annibale (^{99})</td>
<td>Italy</td>
<td>2011</td>
<td>24</td>
<td>268</td>
<td>30</td>
<td>28</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Isegaki (^{100})</td>
<td>Japan</td>
<td>2011</td>
<td>61</td>
<td>480</td>
<td>81</td>
<td>42</td>
<td>0</td>
<td>13</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Uyama (^{101})</td>
<td>Japan</td>
<td>2012</td>
<td>25</td>
<td>361</td>
<td>52</td>
<td>44</td>
<td>0</td>
<td>12</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: EBL, estimated blood loss; LNs, lymph nodes; LOS, length of hospital stay; OT, operative time.

### TABLE 8-5: STUDIES COMPARING ROBOTIC GASTRECTOMY WITH LAPAROSCOPIC AND OPEN APPROACHES FOR TREATMENT OF GASTRIC CANCER
The largest study overall and the only multi-institutional prospective comparative study was conducted in South Korea. These and other studies demonstrate robotic gastrectomy for gastric cancer to provide the same minimally invasive benefits to the patient as laparoscopic surgery over open approaches and include less intraoperative blood loss, shorter hospital stay, decreased use of pain medicine, and early return of gastrointestinal function. When compared to laparoscopy, there are no significant differences in the average number of lymph nodes retrieved, percentage of positive surgical margins, or long-term survival, representing adherence to oncologic principals during surgery without compromise in oncologic outcome. However, the robotic approach for gastric cancer, as for treatment of other diseases, has repeatedly been shown to have longer operative times and higher costs.

Another notable advantage of robotic surgery for gastric cancer is its learning curve. Similar to other studies evaluating the learning curve of robotic surgery versus laparoscopic approach to numerous procedures, the learning curve of robotic radical gastrectomy seems to demonstrate an easier and quicker adaptation when compared to laparoscopy. A shorter robotic
gastrectomy learning curve for an already complex and difficult procedure can increase the number of surgeons who are willing and able to offer a minimally invasive approach and its benefits to patients with gastric cancer.

Thorough understanding of principles of gastric cancer treatment, including strict adherence to the oncologic principles, and proper training in robotic gastric cancer surgery are the keys to providing the benefits of short-term robotic surgical outcomes and ensuring the long-term survival benefits of a proper cancer operation.

**Total Mesorectal Excision for Rectal Cancer: Lower Conversion Rates and Ease of Adoption**

Total mesorectal excision (TME), the standard surgical technique for locally advanced low rectal cancer, is a technically difficult procedure due to the meticulous dissections that are required in a narrow pelvis for preservation of the autonomic nerves and the mesorectal fascial envelope. The technical challenges of a TME are even more pronounced during laparoscopy, which has limited the broad adoption of minimally invasive surgery for rectal cancer operations for over a decade. With the introduction of the robotic surgical systems, surgeons have employed robotic assistance as an alternative minimally invasive approach to overcome some of the challenges of laparoscopic rectal surgery.

Randomized controlled trials have validated the postoperative benefits of laparoscopic rectal surgery along with its oncologic safety. However, due to the technical difficulty of the procedure and limitations of laparoscopic instruments, surgeons performing laparoscopic nerve-sparing TME have experienced an initial high conversion rate of 34% (mean, 14.5%; range, 0%-35%) and high positive circumferential margins (12%). Similar to the challenges faced by gastric cancer surgeons with D2 lymphadenectomy, colorectal surgeons report that laparoscopic TME for cancer is feasible but technically difficult with a steep learning curve (50-150 cases). In contrast, the conversions rates for robotic TME are reported to be between 0% and 9.8% and the learning curve to be less than 20 cases. With consistently lower rates of open conversions and shorter learning curves, robotic surgical platforms may enable an increasing number of surgeons to perform TMEs for rectal cancer.
Those who perform robotic colorectal surgery emphasize the surgical advantages gained from the enhanced features of the robotic surgical systems, especially the surgeon-controlled 3D optics and steady retraction during robotic TME. Since the initial experience of robotic rectal resection 10 years ago in 2003 by Delaney et al\textsuperscript{129} and the first case report of low anterior resection with TME with nerve preservation reported in 2007, several other studies evaluating the application of robotic assistance in performing TME have been conducted (Table 8-6).\textsuperscript{130-136} A study from Korea and another from Italy demonstrated the reduced rate of open conversion in robotic TME when compared to the laparoscopic approach. All studies showed no differences in morbidity, number of retrieved lymph nodes, circumferential margin positivity, and length of hospital stay. The only randomized study of 18 patients treated with robotic tumor-specific mesorectal excision or conventional laparoscopic surgery by Baik et al\textsuperscript{137} reported a significantly shorter length of stay (8.7 ± 1.3 days vs 6.9 ± 1.3 days; \(P < .001\)) with no difference in operative time or conversion rate.

### TABLE 8-6: SELECTED OUTCOMES FOR ROBOTIC TOTAL MESORECTAL EXCISION COMPARED WITH LAPAROSCOPIC APPROACH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Approach</th>
<th>No. of Patients\textsuperscript{a}</th>
<th>Op Time</th>
<th>Conversion Rate (%)</th>
<th>Positive CRM (%)</th>
<th>No. of LNs</th>
<th>LOS (days)</th>
<th>Leak Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patriuti et al,\textsuperscript{128} \textsuperscript{2009}</td>
<td>Italy</td>
<td>Hybrid</td>
<td>29</td>
<td>203</td>
<td>0\textsuperscript{b}</td>
<td>0</td>
<td>10.3</td>
<td>7</td>
<td>6.8</td>
</tr>
<tr>
<td>Baik et al,\textsuperscript{129} \textsuperscript{2009}</td>
<td>Korea</td>
<td>Hybrid</td>
<td>56</td>
<td>178</td>
<td>0\textsuperscript{b}</td>
<td>7.2</td>
<td>17.5</td>
<td>5</td>
<td>1.7</td>
</tr>
<tr>
<td>Bianchi et al,\textsuperscript{130-136} \textsuperscript{2010}</td>
<td>Italy</td>
<td>Totally robotic</td>
<td>25</td>
<td>240</td>
<td>0</td>
<td>8.8</td>
<td>17</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Park JS et al,\textsuperscript{132} \textsuperscript{2011}</td>
<td>Korea</td>
<td>Hybrid</td>
<td>41</td>
<td>231\textsuperscript{b}</td>
<td>0</td>
<td>1.2</td>
<td>17.3</td>
<td>9.9</td>
<td>9.7</td>
</tr>
<tr>
<td>Baek et al,\textsuperscript{133} \textsuperscript{2011}</td>
<td>United States</td>
<td>Hybrid</td>
<td>41</td>
<td>296</td>
<td>7.3</td>
<td>4.9</td>
<td>13.1</td>
<td>6.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Kwak et al,\textsuperscript{133} \textsuperscript{2011}</td>
<td>Korea</td>
<td>Hybrid</td>
<td>59</td>
<td>270\textsuperscript{b}</td>
<td>0</td>
<td>1.7</td>
<td>20</td>
<td>NR</td>
<td>13.5</td>
</tr>
<tr>
<td>D’Annibale et al,\textsuperscript{134} \textsuperscript{2013}</td>
<td>Italy</td>
<td>Totally robotic</td>
<td>50</td>
<td>270</td>
<td>0</td>
<td>0</td>
<td>16.5</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: CRM, circumferential resection margin; LNs, lymph nodes; LOS, length of hospital stay; NR, not reported.
\textsuperscript{a}Table includes comparative studies with \(\geq 20\) patients.
\textsuperscript{b}\(P \leq .05\).

Two meta-analyses are available to provide an overview of the available studies.\textsuperscript{138,139} A meta-analysis by Trastulli et al\textsuperscript{134} of 8 studies comparing
Robotic versus laparoscopic rectal cancer resections found an open conversion rate from robotic rectal surgery of 2% compared to 7.5% in the laparoscopic group ($P = .0007$). While operative times were longer in the robotic group than the laparoscopic group, the leak rates (6.4% vs 6.8%) and overall complication rates (19.7% vs 18.8%) were comparable. A more recent study analyzing 4 randomized controlled trials comparing robotic (n = 111) versus laparoscopic (n = 117) rectal surgery with TME, which included the Baik trial, revealed significantly lower blood losses, conversion rates, and times to recovery of bowel function for the robotic rectal surgery.

A subpopulation of patients who may particularly benefit from robotic versus laparoscopic TME is obese patients. Obesity increases the rate of open conversion from laparoscopic surgery, increases circumferential margin positivity, and results in worse clinical and oncologic outcomes. Analysis of 30 obese patients and 72 nonobese patients who received robotic TME revealed no statistical difference in circumferential margin positivity (3.3% vs 1.3%, $P = 1$) and anastomotic leak rates (3.3% vs 7.3%, $P = 1$) and a trend toward increased open conversion in the obese group (10% vs 2.5%, $P = .15$). High-level evidence comparing robotic versus laparoscopic surgery for rectal cancer will be available from the results of the ROLARR trial, an international multicenter randomized controlled trial.

In the past decade, surgeons using the robotic platforms of the da Vinci systems have demonstrated safety, feasibility, and comparable clinical outcomes for their patients when compared to the laparoscopic approach. Robotic surgeons uniformly acknowledge the significant operative advantage afforded by the enhanced features of robotic surgical platforms when performing complex minimally invasive operations such as the RAHM, robotic D2 lymphadenectomy, and robotic TME. Furthermore, robotic surgery has a quicker learning curve and adaptation to minimally invasive surgery compared with the laparoscopic approach, introducing the possibility of broader adaptability of minimally invasive surgery for more complex abdominal operations. Robotic surgery grants surgeons another option of offering minimally invasive surgery and its benefits to their patients.

Much like when laparoscopy began to challenge the century-old tradition of open operations, the controversy over the efficiency of complex robotic operations when compared to the laparoscopic approach will continue to fuel debate and lead to additional studies. As the disadvantages of longer
operative time, limited training opportunities, and increased cost of the new technology are still being addressed, the decision to perform robotic gastrointestinal operations is based largely on the perceived advantages for the surgeon and the expected improved postoperative patient outcomes of minimally invasive surgery in general.

DECISION TO USE THE ROBOTIC APPROACH

For now, a surgeon’s decision about whether or not to offer a robotic operation for surgical diseases of the gastrointestinal tract is based on the surgeon’s access to the robotic system and his or her knowledge, training, and experience. For over 100 years, the sole surgical approach was the conventional open method. In more recent years, with the application of laparoscopy and then with robotics, there is an additional level of decision making that is required when a surgeon thinks about how he or she will perform the necessary operation, whether it will be an open, laparoscopic, or robotic approach, and when and why he or she will offer the robotic approach over conventional laparoscopy or traditional open operations.

To have the robotic option and to be able to offer a choice to the patient, the surgeon must first decide to incorporate robotic surgery into his or her practice, become familiar with the robotic surgical platform (Fig. 8-3) and the appropriate use and application of the robotic instruments, and understand the technologic advantages it may offer. Second, he or she must be well trained on the use of the robotic surgical system and the selected robotic procedures and create a well-trained robotic operating room team (bedside assistant, scrub nurse, circulator). Third, he or she should critically evaluate the results of available studies. Fourth, the surgeon should constantly reevaluate and self-assess. Fifth, the surgeon should determine the benefits and disadvantages of the robotic approach in his or her own hands.
FUTURE APPLICATIONS

The application robotic technology in gastrointestinal surgery is in its nascent stages. With only 1 company producing robotic surgical platforms, less than 5% of general surgery being performed with robotic assistance, and only 20% of all robotic surgery being performed by general surgeons, the optimal translation of the robotic technology into clinical surgical practice has yet to be reached. Even in the current da Vinci Surgical Systems, several innovative features exist that have yet to find wide utility. For example, the Tilepro
program on all the da Vinci surgical systems offers the potential to integrate multiple views into the surgeon’s console screen and the assistant’s monitors to provide real-time view of the operative field, along with other real-time images such as intraoperative ultrasound findings or intraoperative endoscopic images. In addition, this same function allows the surgeon to view preoperatively obtained images such as a computed tomography scan of the patient or an angiogram of the abdominal vasculature.

In addition, the robotic camera has near-infrared viewing capabilities, a feature that can easily be turned on and off during an operation. After injection of indocyanine green, its uptake can be visualized during the operation to identify vessels, the biliary tree, and lymph nodes depending on the timing and mode of injection. Preliminary reports of the use of fluorescence imaging during robotic gastrointestinal surgery have demonstrated that near-infrared imaging can be used to identify the perfusion of the rectal stump during colorectal surgery, helping surgeons identify proper resection margin to avoid devascularized anastomoses. The proper clinical applications of these features of robotic technology have potential to increase patient safety and surgeon’s efficiency during the operation.

CONCLUSIONS

Robotic surgery for gastrointestinal procedures promises the advantages of novel technology with potential for significant benefits to the general surgeons and our patients. So far, robotic gastrointestinal surgery has been found to be safe and feasible and to provide perceived advantages to the surgeon with an improved learning curve for the approach over laparoscopy. Moreover, robotic surgery demonstrates clinical outcomes equivalent those of laparoscopic surgery. No doubt the technology is superior to that provided by laparoscopic instruments. However, the future of robotic surgery will depend on the surgeon’s ability to translate the technology into meaningful and specific benefits for the patients.

REFERENCES

2. Ballantyne GH. Robotic surgery, telerobotic surgery, telepresence, and telementoring. Review of


Hypertrophic pyloric stenosis occurs in 1.5 to 4 in 1000 live births, and more recent population-based studies suggest the incidence is decreasing over time. It remains a common cause of neonatal emesis and typically presents in the third to fifth week of life. The emesis is typically nonbilious and projectile, although some jaundiced infants may have emesis that has bilious appearance. Hypertrophic pyloric stenosis (HPS) occurs more frequently in male newborns, although providers should be aware that a patient whose mother had pyloric stenosis as an infant has a fourfold incidence of HPS. The precise etiology of the hypertrophied pylorus is unclear, but what was once thought to be an inherently congenital problem is now understood to be an acquired condition. The causes of pyloric stenosis are likely multifactorial, including both genetic and environmental causes. Caretakers often describe projectile nonbilious vomiting and infants present with dehydration and electrolyte imbalances. Physical exam may reveal a sunken fontanelle, lethargy, visible intestinal peristalsis, and in some infants a palpable “olive.”
The “olive” is frequently appreciated by experienced examiners. A nasogastric tube is sometimes necessary to decompress the stomach while the hungry child is calmed by being allowed to drink glucose water, thereby allowing an exam which reveals the presence of an “olive.” The exam is best performed by standing to the right of the child, placing the left hand behind the lower back, and palpating just to the left of the midline with the right hand. The primary physiologic disturbance is hypokalemic hypochloremic metabolic alkalosis, which occurs due to the gastric losses from unremitting emesis. Evaluation should include a renal function panel and imaging. At centers where immediate ultrasound is not available and an “olive” is not palpated, an upper gastrointestinal (UGI) study may be obtained to delineate the obstruction and hypertrophied pylorus. Although exact size criteria vary by institution, it is commonly accepted that muscle wall thickness greater than 3 mm and length greater than 14 mm is abnormal in infants under 30 days old (Fig. 9-1). Infants who are diagnosed with pyloric stenosis must be adequately resuscitated before proceeding to the operating room for pyloromyotomy. The anesthetic risk is heightened when the patient’s bicarbonate level is 30 or greater, as the body attempts to compensate for the metabolic alkalosis with respiratory acidosis, which is accomplished with decreased respiratory drive or hypoventilation. Resuscitation goals should include correcting the metabolic alkalosis and additional electrolyte disturbances such as hypokalemia. Infants should be voiding adequately as a marker of resuscitation as well prior to the operating room. The surgical treatment of HPS is a pyloromyotomy performed laparoscopically or open. The pylorus is incised longitudinally so as to divide the hypertrophic fibers, but avoiding perforation of the mucosa. The hypertrophied wall is then spread until the entire length of the pylorus allows for bulging of the mucosa from the circular muscle fiber of the stomach to just proximal to the duodenum (Fig. 9-2). The risk for perforation is highest at the duodenal end of the pyloromyotomy, and standard teaching suggests that ongoing feeding intolerance following operation is associated with inadequate proximal pyloromyotomy. Inspection of the mucosa can detect bile if a perforation occurred, and some surgeons will also test the pyloromyotomy with insufflation of the stomach while clamping the duodenum distally. If a perforation is identified, the opening should be closed by approximating the mucosa to the seromuscular edge. Patients often do well postoperatively and are best fed ad lib, or on a fast feeding protocol to reach goal in order to
allow for discharge home. Many patients have emesis postoperatively due to edema of the pylorus after manipulation, and parents should be prepared for this expected outcome. Postoperative ultrasound and UGI will demarcate persistent pyloric stenosis even in the setting of adequate pyloromyotomy. Thus, in most cases, watchful waiting is the best course of action with postoperative feeding intolerance. If a perforation has occurred intraoperatively, patients are left with a nasogastric tube and a UGI is performed postoperatively with feeding advancement once a negative study is obtained.

FIGURE 9-1 Pyloric channel visualized by ultrasound showing an elongated, thickened pylorus highly suggestive of pyloric stenosis. Pyloric length greater than 14 mm and thickness greater than 3 mm are considered criteria diagnostic for pyloric stenosis on ultrasound.
FIGURE 9-2  Laparoscopic pyloromyotomy showing spreading of the muscle fibers using blunt graspers. Adequate myotomy is done when the mucosa can be seen bulging through the myotomy and the two sides of muscle can be moved against each other without any restriction.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most common surgical emergency in the neonate and can have lifelong morbidity for affected newborns. NEC is an acquired disease mostly of extremely low birth weight infants (<1000 g). Other risk factors include patent ductus arteriosus treated with indomethacin and enteral feeding with formula. Extensive research has demonstrated the relationship of inflammatory factors, bacterial insults, immune alterations, and environmental genetic roles that may give rise to the mucosal insult in NEC. Providers should be aware of the clinical presentation of an infant with NEC including blood in the stool, bilious emesis, abdominal distention, and abdominal wall discoloration (Fig. 9-3). Neonates may also present with hemodynamic instability, respiratory failure, apnea, bradycardia, neutropenia, leukocytosis, thrombocytopenia, and metabolic acidosis. Plain film radiographs may reveal dilated intestinal loops, bowel wall thickening, pneumatosis intestinalis, portal venous gas, and free peritoneal air. Ultrasound may demonstrate similar findings.
The majority of infants are treated with medical management including discontinuation of enteral feeding, nasogastric decompression, resuscitation, correction of electrolyte abnormalities, and antibiotic initiation. Indications for operative treatment include decline in hemodynamic stability, worsening physical exam, or pneumoperitoneum. The objective in operative treatment is to diagnose the source of sepsis and resect necrotic bowel, and may include a second-look operation in order to limit bowel resection (Fig. 9-4). The patient may be left with one or multiple enterostomies. In unstable low birth weight infants, a drain may be placed in the right lower quadrant in lieu of a formal operation. Most neonates will physiologically improve following drain placement. However, some may go on to decline clinically, and in this case a formal exploration is indicated. Postop care should focus on stabilizing the patient and providing parenteral nutrition, with the plan to close the
enterostomy at 6 to 8 weeks after the initial resection. Contrast study is utilized to evaluate for distal points of obstruction since it is common for strictures to form in NEC despite an initial grossly normal appearance of the distal bowel.

FIGURE 9-4 Intraoperative finding of thinned, necrotic intestinal wall in a neonate affected by NEC.
Short Bowel Syndrome

Short bowel syndrome (SBS) is a condition in which an impaired or limited length of intestine reduces the absorption of nutrients from enteral sources. SBS can occur due to loss of bowel length in the setting of NEC, midgut volvulus, gastroschisis, and with bowel dysfunction such as with motility disorders. The actual length may vary in those pediatric patients affected by SBS, and is impacted positively by the presence of the ileocecal valve as well as a functional colon. Patients with SBS are dependent on total parenteral nutrition (TPN) and may eventually tolerate feeds entirely via an enteral route. The ability to tolerate enteral feeds is dependent on the proportion of small bowel remaining when compared to that expected. Bowel lengthening procedures such as the serial transverse enteroplasty (STEP) and Bianchi procedures depend on the fact that the bowel dilates in the setting of SBS. Such bowel lengthening procedures, along with the development of optimal medical management–associated emergence of centers with SBS programs have been shown to enhance survival in patients with SBS. When necessary, small bowel transplantation, sometimes with liver transplantation, is an option, with an improving 5-year survival in patients with refractory SBS and/or liver failure.

Severe Reflux/Gastrointestinal Reflux Disease

Gastrointestinal reflux disease (GERD) is a relatively common diagnosis in pediatric patients, and as many as 7% of children and infants are diagnosed with GERD. Infants present to the pediatrician with symptoms of reflux including emesis, retching, back arching, and sometimes more severe symptoms such as apparent life-threatening events (ALTE). Many infants and children experience physiologic reflux, which is not considered pathologic. However, if reflux interferes with adequate nutrition and growth or causes aspiration, esophagitis, or hospitalization, medical intervention should be initiated. Medical treatment may not be effective for all infants and children with GERD, and surgical intervention is considered for these patients. It is not entirely understood why some otherwise normal children develop pathological GERD. Children with esophageal atresia (EA), congenital heart defects, and neurological impairment experience an increased incidence of GERD. The Nissen fundoplication is indicated in children with failed medical
management of GERD and who are at risk for complications of reflux if left untreated. The fundoplication is performed laparoscopically or open, and a 360-degree wrap is typically performed. However, in some cases where the esophagus is dysfunctional (such as with EA), or where the patient’s stomach may be small or tubular in shape, a partial wrap, such as a Thal wrap, may be considered. Outcomes favor surgical intervention over long-term medical management. However, the evidence is limited to retrospective data without long-term outcomes. It should be recognized that many children, especially <1 year of age, may simply grow out of their reflux and may not need fundoplication.

ABDOMINAL WALL DEFECTS

Gastroschisis

Gastroschisis is an abdominal wall defect that occurs in the developing embryo and is thought to be a failure of the lateral folds to completely approximate. It affects approximately 5 in 10,000 infants and is associated with maternal factors such as low socioeconomic status, use of tobacco, low maternal age, environmental exposures such as solvents, colorants, and medications such as cyclooxygenase inhibitors and decongestants. Prenatal diagnosis is made via in utero ultrasound. At one time the thought was that Cesarean section may be indicated to prevent injury to the exposed bowel. However, there are no data to support either early vaginal or Cesarean section delivery. Most infants do not have associated anomalies, and of those that do, intestinal atresia is the most common, occurring in 10% to 15% of patients with gastroschisis.

The infant with gastroschisis should be delivered in a center with a neonatal ICU and access to pediatric surgery. A nasogastric tube should be placed to decompress the bowel. Dehydration and hypothermia from insensible fluid and heat losses are prevented by immediate administration of intravenous fluids, wrapping the viscera with a moist gauze dressing, and placement of the lower portion of the newborn’s body in a bowel bag. The viscera should be supported so that they remain on top of the abdomen, rather than falling over to the side, to avoid venous outflow obstruction, which can augment bowel edema. Broad-spectrum antibiotics are administered.
Once the infant is resuscitated, the viscera are examined for evidence of atresia, mesenteric injury, or bowel compromise. Rectal irrigation is often performed to aid in evacuating meconium to reduce the visceral volume, and a Foley catheter is inserted to decompress the bladder. The bowel is often thickened, probably due to contact with the amniotic fluid, such that individual bowel loops are poorly defined (Fig. 9-5). If an atresia is suspected at the time of birth, primary abdominal wall closure is still first achieved in the majority of patients. If an atresia is then confirmed in the postnatal period, re-exploration with repair of the atresia should be performed at 3 to 6 weeks. In some circumstances, an enterostomy is required, especially in the setting of obvious atresia or compromised bowel.

![Image](image.png)

**FIGURE 9-5** Gastrochisis patient with bowel that appears matted together.

Primary closure of the abdominal wall is successful in approximately 80% of newborns. “Sutureless” closure using the umbilical stalk may be successful in neonates with adequate abdominal wall compliance and a small defect (Fig. 9-6). While the fascia has traditionally been closed with sutures at birth,
recent experience has suggested success with using the umbilicus to patch the fascial defect. During attempted reduction of the viscera, it is vital to recognize any compromise in physiologic status of the neonate during closure such as significant increase in airway pressures, unstable hemodynamics, or development of acidosis due to excess intra-abdominal pressure. Examination of the newborn’s lower body may demonstrate edema and cyanosis due to venous congestion. If signs of increased abdominal pressure are observed, the bowel should be removed to decompress the abdomen and a silo placed.
FIGURE 9-6  A. Viable bowel being reduced into the abdominal cavity. B. Reduced bowel without concern for excessive tension on the abdominal wall. C. Closure of the abdominal wall defect with umbilical stalk; also called “sutureless” closure.

If the bowel cannot be safely reduced, a staged closure using a prosthesis is useful (Fig. 9-7). Spring-loaded, preformed silos are now available in different sizes and are easy to place, which precludes the need to manually construct a silo. In some cases, the abdominal wall defect is enlarged to avoid a funnel type configuration of the silo, which could lead to compression of the bowel at the base of the silo with ischemia and necrosis. The silo is wrapped in betadine-moistened gauze to prevent infection and suspended from the over-bed warmer in order to encourage gravity-assisted reduction of the remaining viscera. The viscera are gradually reduced by compressing or twisting the silo and tying an umbilical tape sequentially lower on the silo once every 12 to 24 hours. Use of a silo may be associated with a decrease in time on the mechanical ventilator and time to initial and full feedings. The viscera are usually reduced within a week such that the base of the silo is flat. The patient is then taken back to the operating room and the fascia closed. The edge of the opening is incised and the fascia identified circumferentially. Vicryl sutures are then placed to close the fascia; this is often done in a horizontal fashion because the tension is less than with a vertical fascial closure. Fascial closure sometimes leads to physiologic compromise. In that case, a Vicryl or a biosynthetic mesh (Surgisis ES; Cook Tissue Engineering Products, Bloomington, IN) may be sewn to the fascia, although a ventral hernia may result. This includes infants in whom the bowel cannot be completely reduced and those with concern for ischemic bowel, because a silo allows one to directly monitor the bowel status.
FIGURE 9-7 Gastroschisis bowel in a silo. A. Closure with mesh pieces
sewn to the fascia and to each other to form a contoured silo for the patient. **B.** Preformed silo with spring loading on the internal portion of the silo.

Following reduction of the viscera, return of GI function often is delayed: median time to initiation of feedings is 15 days, with full enteral intake achieved by 22 days. Nearly all patients with gastroschisis require nutritional support with parenteral nutrition and central venous access. Postoperative bowel obstruction is relatively uncommon, and an upper GI contrast study is performed after approximately 2 to 3 weeks when GI function fails to normalize. If the silo separates from the fascia, a pseudomembrane has usually formed beneath the silo, which can be allowed to granulate. Skin graft closure of the abdominal wall is possible once infection has been resolved using topical silver sulfadiazine.

Survival is over 90%. However, the complications that arise pose a considerable threat in the neonate with gastroschisis. NEC may occur during advancement of enteral feeds after gastroschisis closure. Neonates with gastroschisis may be at increased risk of developing NEC due to enhanced mucosal permeability, intestinal dysmotility, or intestinal atresia. Patients with gastroschisis who develop NEC have lower birth weight and are more likely to be formula fed. An enterocutaneous fistula may develop from an anastomotic leak or intestinal injury. Malrotation, if not corrected at the time of the initial operation, may rarely result in jejunal obstruction due to Ladd bands or volvulus. SBS may occur as a result of bowel dysfunction or loss of bowel due to atresia or one of the complications outlined previously. By 6 months of age, intestinal function, in general, has returned to normal. GERD is observed in 16% of patients with gastroschisis, likely related to the presence of increased intra-abdominal pressure.

**Omphalocele**

Omphalocele differs from gastroschisis in that it consists of an abdominal wall defect at the umbilicus, a peritoneal and amnion covering or sac, a normal umbilical cord that attaches to the sac, and umbilical vessels that radiate over the defect (**Fig. 9-8**). Patients with omphalocele have a ruptured sac in approximately 10% of cases; however, the underlying diagnosis is still contrasted from gastroschisis due to the characteristics noted above. The liver is within the defect in approximately half of the patients.
Approximately 30% to 60% of newborns with omphalocele present with concomitant anomalies which may be a source of major morbidity and mortality. Congenital heart disease occurs in 20%, abnormal karyotypes are observed in 29%, and the Beckwith–Wiedemann syndrome is seen in 10% of patients. Patients with Beckwith–Wiedemann may have macroglossia, leading to airway obstruction, and may also present with hypoglycemia, which requires prompt preoperative recognition and treatment.

The initial management of omphalocele is similar to that described for gastroschisis. Hypothermia and dehydration are avoided and treatment with broad-spectrum antibiotics is initiated. Endotracheal intubation and mechanical ventilation may be required if respiratory distress is present, often related to underlying pulmonary hypoplasia. Infants born with giant or large omphalocele greater than 4 to 6 cm in size and/or having the liver in a central position have an increased association with pulmonary hypoplasia and respiratory distress and therefore may require prolonged support with mechanical ventilation. During initial resuscitation, the sac is left intact and is covered with saline-soaked gauze to prevent desiccation and to decrease heat and fluid losses. Evaluation for other chromosomal and developmental
anomalies, especially those related to congenital heart disease, is undertaken.

If the defect is <4 cm in size, it is considered a hernia of the umbilical cord. Closure of a defect of this size is often straightforward and may be amenable to primary closure. Omphaloceles >4 cm are typically more challenging and complicated to manage, and are associated with a poorly developed peritoneal cavity (Fig. 9-4). Skin coverage of the omphalocele defect is the primary goal.

Traditionally, the omphalocele sac is excised during staged reduction, except for where it is adherent to the liver. Excision of the sac in that location could result in liver injury and bleeding. Should bleeding occur, pressure and clot-enhancing agents should be applied. Unfortunately, once the sac is excised, there is time pressure to achieve visceral reduction. Instead, surgeons have recommended leaving the sac intact and sequentially gathering the sac to achieve reduction (Fig. 9-9). Once reduction is accomplished, the fascia may be closed as described for a gastroschisis. A currently popular approach is to use external compression by wrapping of the omphalocele to augment reduction of the viscera while allowing the sac to epithelialize over several months. Application of Silvadene rather than mercurochrome, which can cause mercury poisoning, results in eschar formation of the sac. Contraction and flattening of the omphalocele is often the result, although a ventral hernia usually remains.
When these approaches do not work, or in the case of a ruptured omphalocele, the skin–amnion junction is incised circumferentially and the fascia mobilized; caution should be exercised when dissecting over the superior aspect of the liver since the hepatic veins are often superficial in this location because of the downward position of the liver in the omphalocele. If care is not exercised, injury to and bleeding from the hepatic veins can result. Examination of the diaphragm should be performed to check for the presence of an associated defect. With a large omphalocele, primary closure is rarely possible. Thus, a silo is created from Dacron-reinforced silastic or Gore-Tex (W.L. Gore and Assoc., Inc.; Newark, DE) and is sewn to the fascial edges. The mesh is sequentially gathered in the midline until the fascial edges are nearly approximated. During this process, one must balance aggressively tightening the mesh with avoiding undue tension on the mesh: excess tension could lead to premature separation of the mesh from the fascia. The patient should also be monitored for evidence of high intraabdominal pressure.
resulting in hypercarbia, oliguria, hemodynamic compromise, and acidosis. Such high pressures could compromise ventilation, renal blood flow, cardiac output, intestinal perfusion, and venous drainage from the lower extremities. Once it is nearly approximated, the fascia can then be closed with removal of the mesh, although a reasonable option is to close the skin while leaving part of the mesh in place. If the mesh separates, granulation tissue often remains underneath. This presents a challenging wound care problem: application of homograft and other artificial wound coverings may be considered. One option is to allow the wound to epithelialize. An alternative is split-thickness skin graft placement, which is often effective once any wound infection is controlled.

As with gastroschisis, return of gastrointestinal function is often delayed in patients with a large omphalocele. Parenteral nutrition is initiated within the first few days of life, requiring early central venous access. Mechanical bowel obstruction can occur, but is unusual. Lung and chest wall hypoplasia and chronic respiratory insufficiency are reasonably common among patients with giant omphaloceles, and tracheostomy tube placement may be required. Staged reduction in patients with giant omphalocele applies pressure upon the diaphragm, which complicates lung dysfunction.

Survival is 80% to 90%, and mortality is impacted primarily by the associated anomalies. In children with omphalocele, the incidence of gastroesophageal reflux (GER) is high (43%), likely due to the elevated intraabdominal pressure. Ventral hernias often result when a nonsurgical approach is employed. A staged approach to closure of the ventral hernia will be required in those with massive ventral hernias. The incidence of cryptorchidism is increased in patients with omphalocele (16%); this is thought to be related to decreased intraabdominal pressure during the typical period of physiologic in-utero testicular descent.

**INTESTINAL OBSTRUCTION IN THE NEONATE**

**Malrotation**

At approximately 8 to 10 weeks of development, the midgut rotates 270
degrees counterclockwise, which leads to fixation of the proximal small bowel at the ligament of Treitz, attachment of the cecum and right colon in the right lower quadrant, and broad fixation of the base of the small bowel mesentery to the retroperitoneum. If this rotation fails to occur, the small intestine remains on the right side of the abdomen, the cecum is typically at a location other than the right lower quadrant, and the bowel remains unfixed. The entire midgut is mobile and prone to rotation on a central axis or volvulus, which is the mode of presentation in 85% of newborns and 31% of patients of all ages. Volvulus may compromise superior mesenteric artery (SMA) inflow and venous blood outflow, leading to ischemia or necrosis of the entire small intestine and transverse colon. In addition, peritoneal bands known as Ladd bands, which are responsible for drawing the cecum into the right lower quadrant, cross over and may partially obstruct the distal duodenum and proximal small bowel. Eighty-nine percent of patients with symptomatic malrotation present in the first year of life, with 50% in the first week and 65% in the first month, leaving only 11% to present after the first year. An occasional older patient presents with intermittent midgut volvulus and recurrent abdominal pain that may mimic other common causes of an acute abdomen.

The failure to recognize this entity promptly may result in the loss of the entire midgut. The primary symptom of acute midgut volvulus is sudden onset of bilious vomiting; therefore it is essential the provider consider the diagnosis of malrotation in any infant with bilious vomiting. With midgut volvulus, as the distal bowel empties, the abdomen is often scaphoid rather than distended. Physical examination is unexpectedly without peritonitis until later in the process when intestinal ischemia and necrosis develop. At that point, abdominal distension, tenderness, and hematochezia are often present. As the course progresses, hypovolemia, shock, and acidosis ensue. To avoid these sequelae, an emergent contrast UGI study should be performed. UGI evaluation of the course of the duodenum demonstrates that the duodenojejunal junction remains to the right of the midline, and the normal posterior and cephalad fixation of the duodenum at the ligament of Treitz is absent (Fig. 9-10). If volvulus is present, a corkscrew appearance of the duodenojejunal junction is noted. Ultrasound may be helpful in diagnosing midgut volvulus by identifying an abnormal SMA and superior mesenteric vein (SMV) relationship as well as inability to identify the duodenum passing behind the SMA.
Midgut volvulus is a surgical emergency. Once the diagnosis of malrotation is made in the symptomatic patient, immediate laparotomy is indicated even if radiologic and clinical signs of volvulus are absent (Fig. 9-11). The child should be rapidly resuscitated either in the operating room or while preparing the operating room. A Ladd procedure consists of the following: (i) exploration of the midgut; (ii) counterclockwise derotation of a midgut volvulus (if present); (iii) performance of a Kocher maneuver with
division of Ladd bands; (iv) broadening of the mesentery of the proximal 
jejunum and the transverse colon by division of adhesions between these two 
structures—along with subsequent general bowel adhesion formation, 
broadening the mesentery will reduce the incidence of recurrent volvulus 
(Fig. 9-12); (v) return of the intestine to the abdomen without any twists in 
the mesentery, and placement of the cecum in the left lower quadrant to 
further broaden the mesentery; and (vi) appendectomy because of the 
potential of a difficult diagnosis of appendicitis in the future with the 
inappropriate location of the appendix. Failure to completely detorse the 
bowel or lyse all of Ladd bands may result in persistent obstruction or 
recurrence of volvulus. There is no evidence to support fixation of the 
intestine to the retroperitoneum. If compromised bowel is noted, a second 
look at 24 hours is an option to minimize the amount of bowel resected and 
short gut syndrome. If the surgeon encounters grossly necrotic bowel it may 
be necessary to resect and plan for reexploration at 24 hours. Performance of 
an ileostomy is usually necessary only if there is continued question of 
testinal viability at reexploration. Necrosis of the entire midgut makes 
survival unlikely; resection of the entire midgut is associated with high 
morbidity and lifelong parenteral nutrition or small bowel transplantation in 
most cases. Postoperative complications may occur such as recurrence of 
midgut volvulus; although infrequent, <2% of patients have recurrence and it 
is thought to be related to a failure to lyse all the Ladd bands. Adhesive 
bowel obstruction occurs in 1% to 10% of patients, and perioperative 
mortality is 4% and is primarily associated with sepsis from massive 
testinal necrosis. Mortality is at least 50% in those with extensive (>75%) 
small bowel infarction. Mortality may be also increased in those with 
congenital heart disease. One review of patients with malrotation and 
heterotaxy identified nearly 10% in-hospital mortality, due to cardiac causes 
in those who underwent a Ladd procedure. However, the authors noted that 
the deaths were not due to the Ladd procedure and that 27% of the patients 
with heterotaxy and symptomatic malrotation had midgut volvulus. In 
another study, 18% of patients with heterotaxy died after a Ladd procedure: 
all deaths occurred more than 1 month after the operation and were due to the 
underlying cardiac disease. It is therefore important for the surgical and 
cardiology teams to discuss the potential risks and benefits of a Ladd 
procedure in patients with congenital heart disease and asymptomatic 
malrotation.
FIGURE 9-11 Malrotation with volvulus: The axis of volvulus is the narrow mesentery of the nonrotated intestine; the segment of intestine to the right appears dusky and compromised secondary to volvulus. Healthy proximal bowel is seen to the left.
FIGURE 9-12 Malrotation after Ladd’s procedure with widening of the mesentery.

**Esophageal Atresia/Tracheoesophageal Fistula**

Providers may be aware of the potential for the diagnosis of esophageal atresia (EA) from a diagnostic ultrasound performed during gestation
demonstrating polyhydramnios. Postnatally, a neonate may have difficulty handling secretions and may have symptoms of choking or coughing with feeding. Usually an unsuccessful attempt is made at passing a nasogastric or orogastric tube. Curling of the tube in the dilated proximal esophageal pouch may be seen on plain radiograph and is pathognomonic for EA (Fig. 9-13). The neonate is always at risk for aspiration, especially if EA goes unrecognized. In addition, gastric secretions may reflux into the lungs through a distal tracheoesophageal fistula (TEF), if present, and lead to further lung contamination and the development of pneumonia. Maintaining the newborn in a strict 30-degree to 45-degree upright position will inhibit reflux of gastrointestinal contents into the tracheobronchial tree. Intravenous antibiotics should be administered prophylactically if the patient exhibits signs of pneumonia. Mechanical ventilation should be performed only if necessary because of the risk of ventilation through a TEF leading to gastric distention, and potentially, perforation. Respiratory insufficiency, especially in the setting of prematurity and respiratory distress syndrome (RDS), may be associated with a decrease in pulmonary compliance. In that setting, the TEF competes with and prevents adequate pulmonary ventilation. Occlusion of the TEF via lower esophageal occlusion with a balloon catheter introduced through a gastrostomy site or thoracotomy with division of the fistula may be required with or without performance of an esophageal anastomosis esophagogastrostomy).
FIGURE 9-13 Esophageal atresia with tracheoesophageal fistula. A replogle tube placed into the proximal pouch that appears to be folding on itself (black arrow). Air within the stomach and bowel is highly suggestive of a communication between the trachea or airway and the gastrointestinal tract,
likely in form of a tracheoesophageal fistula.

Air in the abdomen on radiograph suggests the presence of a distal TEF (85%), and the absence of distal air indicates a pure EA (7%) (Fig. 9-14). Radiologic evaluation, performed with careful administration of contrast medium into the upper pouch with the patient sitting upright to avoid aspiration, will verify the diagnosis of EA and identify a proximal TEF, which is present in approximately 1% of patients. Proximal fistulas are frequently missed at the time of operation because the fistula may be proximal, above the level of routine dissection. The presence of a small proximal pouch suggests that a proximal fistula may be present and that the anastomosis may be under tension. Bronchoscopy may help to identify a proximal fistula in the operating room prior to repair of the EA/TEF. However, bronchoscopy may miss small proximal fistulas, and contrast study of the proximal pouch appears to be an equally useful adjunctive test with low risk of aspiration when appropriately performed (Fig. 9-15).
FIGURE 9-14  Pure esophageal atresia. A replogle is seen coiled in the proximal pouch (white arrow). There is a paucity or lack of air in the stomach or bowel, suggestive of lack of a fistula between the trachea and esophagus.
Greater than half of the patients with EA/TEF have associated anomalies. Approximately 15% of patients have a constellation of findings compatible
with the VATER or VACTERL association (vertebral defects, anal atresia, cardiac anomalies, TEF and EA, renal defects, and limb abnormalities). The most common anomalies are cardiac (38%) and are responsible for many of the deaths associated with EA and TEF. Renal anomalies occur in 17% of patients.

In general, patients with EA and a distal TEF have adequate esophageal length to allow primary reconstruction. A repair is generally planned within the first 24 to 48 hours unless contraindicated by prematurity, the presence of congenital heart disease, or critical illness rendering the operative and anesthetic risks unacceptable. In that case, temporizing with proximal pouch replogle suction and a gastrostomy tube with plans for delayed repair may be the best strategy. When repair is performed, an approach through the right chest using a muscle-sparing incision is typically performed with access via the fourth intercostal space. The presence of a right aortic arch, found in 2% of patients with the EA/TEF anomaly, should be identified on echocardiography so that the surgical team can consider a left thoracic approach. A retopleural approach is historically used in order to contain a potential leak, although there is no evidence to suggest that such an approach is beneficial. The distal TEF is identified in the region of the carina and is divided. Prior to division of the fistula, maintenance of oxygenation may be tenuous and requires that the surgeon intermittently allow expansion of the right lung; this problem usually resolves once the fistula is ligated. A few millimeters of esophageal tissue are left on the trachea during division of the TEF in order to avoid compromise of the tracheal lumen. The tracheal closure is checked for an air leak with saline submersion and application of sustained airway pressure. The distal esophagus can be mobilized with minimal risk of devascularization. The proximal esophageal pouch can be identified by having the anesthesiologist advance a catheter placed through the mouth into the pouch. A suture is placed in the apex of the proximal pouch for manipulation in order to avoid trauma due to repeated grasping of the tissue. The pouch is mobilized in the upper mediastinum; care is taken while mobilizing the anterior esophagus because of the risk of entry into the membranous trachea. Use of cautery should be limited, especially in the apex of the thorax, because of the risk of thermal injury to the recurrent laryngeal nerves. An esophagoesophageostomy is performed, taking care to ensure that sutures include the full thickness of the esophagus. Some patients with EA and a distal TEF will have a longer gap between the proximal and distal
esophagus (>2 vertebral bodies). The anastomosis may be performed under tension. Some surgeons maintain the patient sedated with the head in flexed position to decrease postoperative anastomotic tension. If the gap between the upper and lower pouches is long enough, the TEF may be ligated and divided and the distal pouch tacked to the prevertebral fascia, with reconstruction performed after 8 to 12 weeks. A nasogastric tube is passed through the anastomosis into the stomach to ensure patency of the distal esophagus. Gastrostomy tubes may be indicated if the presence of other anomalies suggests that prolonged tube feeding will be required. A drainage tube is typically placed near, but not on, the anastomosis at the end of the operation to contain postoperative anastomotic leaks. Small openings in the pleura are unimportant and should not be closed when a retropleural approach is used. Oropharyngeal suctioning is limited to <6 cm from the lips in order to avoid trauma to the anastomosis. An esophageal contrast study is performed approximately 1 week after operation. If the anastomosis is intact, feedings are initiated, antibiotics are discontinued, and the retropleural chest tube is removed. Complications include anastomotic leaks, which occur in 16% of cases and typically resolve without intervention. Silk sutures are associated with a two- to threefold increase in the incidence of anastomotic leak. Postoperative strictures may be found in up to 40% of cases and are often associated with leaks, anastomotic tension, and GER. GER occurs in up to 70% of patients with EA/TEF and may require a fundoplication, which may result in dysphagia by augmenting the esophageal dysfunction typically associated with an EA/TEF.

In patients with isolated EA without a TEF (pure esophageal atresia), the distal esophagus is typically short, which precludes immediate repair. Patients with pure esophageal atresia that are not amenable to a primary approach may be repaired at 8 to 12 weeks with a delayed primary anastomosis. The management involves initial placement of a gastrostomy tube, allowing for growth of the proximal and distal pouch over the ensuing 3 months prior to an attempt at a primary repair (Fig. 9-16). Daily dilation of the proximal pouch may enhance lengthening. There are other alternative approaches that may be required, including proximal pouch myotomies to extend length. However, these may be associated with complications such as leaks, strictures, outpouching of the esophagus at the site of the myotomy, and esophageal dysfunction. In patients with very long gaps, replacement of the esophagus with a natural conduit such as the stomach, colon, or even the
small bowel may be the best option.

**FIGURE 9-16** A. Gap assessment done in pure esophageal atresia at 1 month of age. This is performed by inserting a pediatric endoscope into the gastrostomy that was created for feeding at the time of diagnosis, and inserting a second radio-opaque dilator or instrument into the proximal pouch at the same time under fluoroscopy. B. Gap assessment at 2 months.

Other techniques are available that may lengthen the esophagus, including the Kimura procedure, in which an esophagostomy is formed on the chest and sequentially lengthened every 2 to 3 weeks by advancing the esophagostomy inferiorly along the chest wall. This technique allows sham feedings, which are important for normal feeding development to take place.

Another more recent approach to augment esophageal length was developed by Foker. With this approach, continuous traction is used to slowly approximate the proximal and distal ends of the esophagus, followed by performance of an anastomosis (Fig. 9-17). The traction is applied by sutures placed on the ends of the esophagus which are brought out through the lateral, superior, and inferior rib interspaces, respectively. Tension is steadily applied to allow for growth and eventual approximation. With the Foker technique, the patient is at risk for postoperative strictures and reflux that can be managed with dilations and fundoplication, respectively. If the sutures pull through the ends of the esophagus there is the potential for esophageal leak.
Options when this complication occurs are to replace the sutures with repair of the leak (if present) or to convert to a cervical esophagostomy with plans for esophageal reconstruction later.

**FIGURE 9-17** Foker procedure: Sutures are placed into the ends of the proximal pouch and the distal esophagus and brought out through the chest externally. These are then tightened intermittently until the two ends of the esophagus are adjacent to each other and the gap is closed.

In general, all attempts are made to salvage the native esophagus. However, when the esophagus cannot be approximated or if complications of stricture, recurrent GER, or esophageal dysfunction persist, esophageal replacement is an alternative. Right or left colon, jejunum, or the stomach, either as a reversed-gastric tube or a gastric transposition, can be used. Although an effective solution to establishing esophageal continuity, the complication rate with esophageal replacement is substantial and includes an anastomotic leak rate of approximately 30%, stricture formation in 20% to 60%, and a mortality of 5%. Anastomotic leaks almost always resolve spontaneously. A variety of options are available for esophageal replacement.
When a colon conduit is used, it can consist of right or left colon and be placed behind the hilum of the lung on either side or in a substernal position, although the latter is associated with a higher stenosis rate. A vagotomy is effective in preventing the development of ulcers when a colon conduit is used. The colon may become redundant in the chest (sink trap deformity), leading to dysfunction and stasis (16%). Reoperation is necessary in approximately 50% of patients and is most often performed to redo the esophagocolic or cologastric anastomoses due to strictures or to correct the redundancy. Gastrocolic reflux may also occur, and approximately 20% will ultimately require replacement of the colon graft, which is best managed by performance of a gastric transposition or a free jejunal graft.

Another option for esophageal replacement is the reverse gastric tube, which is formed by creating a tube from the greater curvature of the stomach. This is most often brought up to the neck through what would have been the esophageal bed. Complications are leak from the long suture line and compromise of the stomach size, especially in newborns with a diminutive stomach. Finally, gastric transposition is a successful option because the blood supply to the stomach is excellent and the operation is technically easier than other alternatives. This option can be used even when previous operations have been performed on the stomach. The right and left gastroepiploic arteries are maintained intact while the stomach is otherwise mobilized. The distal esophageal segment is excised and the fundus is brought through the posterior mediastinum, which limits the potential complication of gastric distension. The posterior aspect of the stomach must be anchored to the sternocleidomastoid muscles in the infant and to the prevertebral fascia in the older patient to prevent retraction of the stomach into the thorax. A pyloromyotomy should be performed to enhance gastric emptying. The dumping syndrome occurs in a minority of patients in the postoperative period but typically resolves over the first year. Care must be taken to avoid a twist in any of the conduits performed, which may result in ischemia or obstruction. Dissection must be maintained on the proximal esophagus to avoid injury to the recurrent laryngeal nerves.

The simultaneous presentation of EA/TEF and duodenal atresia is a challenging clinical situation. Duodenal atresia occurs in 10% of patients with isolated EA, and the lack of air in the GI tract in the setting of EA without a TEF can delay the diagnosis of duodenal atresia until a gastrostomy tube is placed. An intraoperative contrast study at the time of gastrostomy
tube placement helps to identify this combined anomaly, although this is not routinely performed. Imperforate anus, which is part of the VACTERL constellation of findings, should be typically addressed by performing a colostomy.

Patients with a TEF but no EA (4%) often have episodes of gastric distention during crying and choking, recurrent pneumonia, and cyanotic spells during feeding. The diagnosis is best made by a contrast swallow or bronchoscopy, which may demonstrate the H-type fistula between the trachea and esophagus. A Fogarty catheter may be placed through the fistula at the time of bronchoscopy to help with identification of the fistula at operation. Ligation of the fistula is usually performed via a right cervical approach. The recurrent laryngeal nerve must be identified to prevent injury, the most common complication of this procedure. Recurrence of the fistula is rare.

Overall survival rate is 95%. Mortality is usually secondary to associated anomalies and is increased with the presence of major cardiac disease and birth weight <1500 g (Table 9-1). One of the most difficult decision-making situations involves the premature newborn with RDS and EA/TEF because the associated ventilator leak through the fistula increases with airway pressure escalation; therefore, ligation of the fistula is ideally performed before compromised respiratory status precludes a safe operation, requiring close monitoring and keen judgement. Early thoracotomy and ligation of the fistula provides an ability to ventilate and prevents gastric distention, though this decision must be weighed against the overall clinical status of the neonate.

**TABLE 9-1: PREDICTORS OF SURVIVAL FROM AN ESOPHAGEAL ATRESIA ANOMALY**
Immediate postoperative complications include small anastomotic leaks on postoperative contrast study in 15% of EA/TEF patients with primary repair. Almost all small leaks will resolve spontaneously with continuation of IV antibiotics and chest tube drainage. A repeat study is performed 1 week later, and oral feedings are held until the leak resolves. Disruption of the anastomosis occurs in approximately 5% due to excess tension, ischemia, or poor surgical technique, and presents with persistent pneumothorax, respiratory distress, pleural effusion, and/or sepsis. The disruption should be managed with either direct repair, preferably with reinforcement of the anastomosis with an intercostal muscle flap or a pleural or pericardial patch, or with formation of a cervical esophagostomy and placement of a gastrostomy tube with subsequent esophageal replacement. Stricture formation occurs in approximately 15% of cases and is often associated with a prior anastomotic leak. Most strictures are responsive to repeated antegrade dilatation initially at a frequency of approximately every 2 to 3 weeks. Esophagoscopy should be performed before dilatation to assess the anastomotic caliber and after to ensure that full-thickness perforation has not occurred. Hurst-Maloney dilators may be sequentially passed to dilate a slightly narrowed stricture. In narrow strictures, a wire passed under endoscopic and/or fluoroscopic guidance will allow safe passage of sequentially larger Savory dilators or balloon dilators under fluoroscopic guidance to safely enlarge the anastomosis. Contrast injection at the end of the dilatation can be performed to identify a leak at the site of the stricture. Occasionally, refractory strictures may require resection or even esophageal resection.

<table>
<thead>
<tr>
<th>Group</th>
<th>Total, n</th>
<th>Dead, n</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Birth weight &gt;1500 g without major congenital heart disease</td>
<td>293</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>II. Birth weight &lt;1500 g or major congenital heart disease</td>
<td>70</td>
<td>29</td>
<td>59</td>
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<td>III. Birth weight &lt;1500 g and major congenital heart disease</td>
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replacement. Refractory strictures may be due to the presence of reflux, which occurs frequently in patients with EA/TEF. Strictures due to GER usually respond to dilatation once a fundoplication has been performed. Thus, the presence of GER should be investigated if a stricture does not respond after two or three dilatations.

Leak from the trachea or compromise of the tracheal lumen is unusual but requires operation in the former and bronchoscopic evaluation in the latter. Recurrent TEF occurs in 3% of cases, is usually associated with a postoperative leak, and requires reoperation. Recurrent pneumonia, coughing, and choking are frequently noted. Esophagram with the patient prone and/or with balloon catheter obstruction of the distal esophagus during esophageal contrast administration can enhance identification of the fistula. Bronchoscopy with attempts at passage of a catheter through a potential fistula or instillation of dilute methylene blue into the trachea with esophageal assessment for the presence of blue dye will frequently reveal the presence of a recurrent TEF. High-resolution CT may help to identify a recurrent fistula or a missed proximal fistula. Thoracotomy with fistula ligation is required. A 2 Fr balloon catheter should first be passed through the fistula under bronchoscopic guidance to allow intraoperative identification of the fistula. Once the fistula is ligated, a pleural or pericardial flap should be interposed between the trachea and esophagus to help prevent recurrence. Injection of fibrin glue into the fistula may result in closure of the communication without thoracotomy.

The most common long-term problems associated with EA include GER (40%–70%), tracheomalacia (16%), and esophageal dysfunction. GER is likely due to the tension placed on the distal esophagus with compromise of the native antireflux mechanisms and shortening of the intra-abdominal esophagus. Recurrent pneumonia, reactive airway disease, cyanotic spells, and persistent anastomotic stricture can be symptoms/signs of GER in the EA/TEF patient. GER symptoms are present in at least 20% to 40% of adult patients with previous EA/TEF. Evaluation with upper GI contrast study and/or 24-hour pH probe may document the diagnosis. GER is typically first managed with prokinetic agents and proton pump inhibitors, although approximately 30% to 40% of patients require a fundoplication. A 360-degree Nissen fundoplication is most frequently performed, although a Nissen fundoplication may exacerbate the esophageal dysfunction associated with EA/TEF. Under those circumstances, recurrent reflux, esophageal
dilation and dysfunction, and dysphagia may result in an adverse outcome. A Thal fundoplication is a reasonable alternative because of the partial nature of the wrap, but the failure rate has been high. As a result, most surgeons prefer to perform a “floppy” Nissen fundoplication. Because studies have demonstrated a relatively high incidence of Barrett’s esophagitis among patients with repaired EA/TEF (5%–7%), long-term endoscopic surveillance is important.

Tracheomalacia results in stridor and a barking cough in newborns, although some patients may present with apnea, as the result of a weakness in the tracheal wall such that the anterior and posterior tracheal walls coapt during expiration. Bronchoscopy during spontaneous breathing demonstrates the collapse in the distal third of the trachea. Mild symptoms in most patients can be followed, with expected resolution as the patient grows. Life-threatening symptoms require operation in 6%. An aortopexy, in which the anterior aspect of the aortic arch is approximated to the posterior sternum, is effective in almost all patients at resolving the symptoms of tracheomalacia. A Palmaz airway stent or tracheostomy may be of benefit should the aortopexy prove to be inadequate. Frequently, it is difficult to determine whether the symptoms observed are due to tracheomalacia or GER.

Esophageal dysmotility is present in the majority of EA/TEF children, and 40% to 75% of adult EA/TEF patients have mild-to-severe dysphagia and esophageal dysmotility. In most cases, the dysphagia is tolerable and in infants can be managed by slowing the pace of feeding and feeding while the patient is sitting up. Scoliosis develops in 8% of patients, probably due to fusion of the ribs at the site of the thoracotomy, which prevents ipsilateral spine growth. Anterior chest wall deformities are observed in 20%, though a muscle sparing or thoracoscopic (see below) approach may decrease the incidence of this complication. Foreign body impaction occurs in 13% of patients with corrected EA/TEF, usually during the child’s first 5 years of life.

A thoracoscopic approach has been advocated by some centers to avoid the complications associated with the thoracotomy. In a multi-institutional retrospective review of 104 patients who underwent thoracoscopic EA/TEF repair, 11.5% developed an early leak or stricture and a third needed esophageal dilation at least once. Two infants developed a recurrent fistula and 24% required a subsequent laparoscopic fundoplication. In another retrospective comparison of the thoracoscopic and open techniques, a
minimally invasive approach allowed decreased postoperative narcotic use, shorter time to extubation, earlier feeding by mouth, and decreased length of stay, without an increase in operative time, anastomotic leak, stricture, or mortality.

**Duodenal Obstruction (Duodenal Atresia)**

Congenital duodenal obstruction occurs in 1 in 5000 to 10,000 live births. Most causes of obstruction are atresia (76%) and duodenal webs (23%). A common area of duodenal obstruction is the second portion of the duodenum, as this site is a hub of embryological activity in the growing fetus. Duodenal atresia results from failure of recanalization of the duodenal lumen, while duodenal stenosis and webs result from incomplete recanalization of the duodenal lumen.

Congenital duodenal obstruction can broadly be divided into intrinsic and extrinsic causes. Intrinsic causes include the presence of a duodenal web (18%), stenosis, or atresia (10%). Extrinsic causes include annular pancreas (36%) or the presence of Ladd bands (36%). Preduodenal portal vein is a rare cause of extrinsic duodenal obstruction (**Fig. 9-18**). These causes develop in the embryological period, intrinsic being specifically tied to the period where recanalization takes place in the proximal gastrointestinal tract (GIT). Both categories may appear similar on diagnostic studies, making distinguishing them difficult until the time of operation.
Duodenal webs occur with an estimated incidence of 1 in 10,000 to 1 in 40,000 live births. Simplistically, webs occur from incomplete recanalization of the duodenum during fetal development, which results in a thin, membranous web of mucosa and submucosa, with the muscular layer being absent. They are often congenital in origin, although NSAIDs have been implicated as a causative agent. Duodenal webs are frequently associated with other congenital anomalies such as Down syndrome (21%) and cardiac anomalies, to name a few.

The presence of a duodenal obstruction may be appreciated on prenatal ultrasound by the presence of polyhydramnios of unspecified etiology, which is seen in about two-thirds of patients, or a dilated stomach and duodenum (ultrasound equivalent of a “double-bubble” seen on x-ray; see below). About half of the patients with duodenal atresia are premature (<37 weeks’ gestation); therefore, issues related to prematurity such as retinopathy, intracranial bleeding, and respiratory insufficiency must also be addressed when present.

Typical presenting symptoms in the first 1 to 2 days of life include feeding
intolerance and emesis, which is usually bilious unless the obstruction is proximal to the ampulla of Vater, which it may be in 5% to 10% of cases. Following birth, plain abdominal radiographs demonstrate the classic “double-bubble” (air-filled, dilated stomach and proximal duodenum with paucity of distal gastrointestinal air) in 77% of patients (Fig. 9-19). Air can be used as a contrast agent by injecting 20 mL through the nasogastric tube during performance of the radiograph. The distal small intestine and colon remain gasless with a duodenal atresia. In contrast, in the setting of a duodenal web with an opening or a malrotation with Ladd bands or volvulus, gas is often present in the downstream GI tract. The importance of the distinction is that the urgency with which operation is performed is reduced if malrotation with volvulus is excluded from the differential. However, in most cases prompt, if not emergent, surgical intervention is still appropriate. If a classic double-bubble is observed, further radiographic study is unnecessary as this has been accepted as a diagnostic sign of duodenal obstruction.
A UGI series is the study of choice if there is concern for malrotation with volvulus. This study can initially be performed with injection of air through the nasogastric tube, as mentioned earlier, followed by serial imaging to monitor progression of the air into the distal GIT. If air is seen distally, this would prompt further investigation with an UGI series with a water-soluble contrast medium such as gastrograffin to rule out malrotation or Ladd’s bands as a potential cause of proximal GIT obstruction. The diagnosis of malrotation is made by examining the position of the duodenojejunal
junction: it should be to the left of the vertebral pedicles, heading posteriorly at the level of the duodenal bulb.

Surgical repair for duodenal obstruction classically consists of a right supraumbilical incision with mobilization of the duodenum with duodenoduodenostomy. However, with technological advances and growing surgical skills, laparoscopic approaches to correction of duodenal obstruction have become more favorable. Regardless of approach, the essential steps to the procedure remain the same. After a Kocher maneuver, the markedly dilated proximal duodenum and the decompressed distal duodenum are identified and mobilized (Fig. 9-20). A duodenoduodenostomy is performed by creating an incision on the dilated proximal duodenum in a horizontal or perpendicular axis to the small bowel and incising the distal decompressed bowel in a longitudinal manner. These incisions are then used to create the duodenoduodenostomy.
FIGURE 9-20 Duodenal obstruction caused by annular pancreas. Proximal dilated portion (A) will be anastomosed to distal collapsed portion (B).

In the case of duodenal webs, the most difficult maneuver involves determining the site of the obstruction, as a “windsock” deformity may be present, making the origin of the atresia or stenosis proximal to the change in caliber of the duodenum. One must be certain that a corrective procedure is not performed distal to the actual site of obstruction. To avoid this complication, a small longitudinal incision may first be made along the anterolateral, distal aspect of the dilated portion of the duodenum. The anterolateral aspect is used in order to avoid the ampulla of Vater during subsequent anastomosis. A catheter is passed proximally and distally to
identify the location of the obstruction. Alternatively, a small gastrotomy may be performed and a catheter passed distally into the duodenum. Gentle pressure applied to the catheter at the site of obstruction may demonstrate the site of attachment of a windsock by the presence of an indentation on the surface of the dilated duodenum.

If a simple web is present, the longitudinal incision can be extended across the anterolateral aspect of the web and the web incised after identification of the ampulla of Vater. Identification of the ampulla is best performed by compressing the gallbladder and observing the site of bile drainage into the duodenum. The ostium of the ampulla of Vater is often located at the base of or even within the web. In most cases excision of the web is ill-advised, and incision of the anterolateral aspect of the web is carefully performed after identification of the ampulla of Vater in order to avoid injury to, or obstruction of, the biliary tract. Incision of the anterolateral aspect of the web is easiest when an opening is present, because the ampulla will be medial to the opening. Transverse closure of the longitudinal incision, as in a Heinike–Mikulicz pyloroplasty, effectively bypasses the obstruction once the web is partially incised. Alternatively, bypass of the obstructing lesion, with a duodenoduodenostomy, is performed. As described earlier, an anastomosis between a transverse incision in the proximal dilated duodenum and a longitudinal incision in the distal duodenum is commonly used. The initial exploratory duodenal incision allows correct placement of the second incision for this anastomosis either distal or proximal, depending on where the obstruction is located. The proximal incision is extended horizontally just above the obstruction and the distal in a longitudinal direction starting just downstream from the obstruction. The proximal duodenal incision is approximately 1 cm in length and maintained on the anterolateral aspect of the duodenum to avoid injury to the biliary tract or the pancreas during suture placement. The distal incision is also approximately 1 cm in length and placed on the antimesenteric border. In the rare circumstance where a wide gap exists between the ends of the duodenum, a loop of proximal jejunum may be brought to the duodenum through the mesocolon for a duodenojejunostomy.

Although rare, a distal atresia is present in up to 3% of cases; thus, in an open procedure the rest of the small bowel should be examined. One approach is to inject saline through the entire bowel via a catheter placed through the duodenal incision prior to anastomosis.
Morbidity and mortality for these infants are frequently due to complications from prematurity, trisomy 21, congenital heart disease, and other associated anomalies. Feeding is often delayed for days to weeks (mean of 13 days) due to duodenal dysfunction in the proximal dilated duodenum. Clinicians may need to increase feeds slowly and to tolerate higher volumes of feeding residuals in the newborn after operation. Some surgeons suggest that placement of a transanastomotic feeding tube at the time of correction of the duodenal atresia allows earlier initiation of feeding, while others suggest otherwise. Some surgeons perform a resection of the redundant duodenum (duodenoplasty) at the time of the initial operation (Fig. 9-21). Rarely is reoperation required in the newborn period. Upper GI contrast studies should be performed only if feeding intolerance persists for a number of weeks. Chromosomes should be assessed for trisomy 21, which is present in 21% of patients with duodenal obstruction.

**FIGURE 9-21** Duodenoplasty done to decrease the amount of redundant duodenum at the time of surgical repair.

Postoperative complications can be divided into early and late complications. Early complications include anastomotic obstruction (3%), congestive heart failure (9%), prolonged ileus (4%), pneumonia (5%), and
superficial wound infection (3%). Late complications include reoperation for adhesive obstruction in 15%, blind loop syndrome or bile reflux gastritis in 22%, GERD unresponsive to medical management that requires antireflux surgery (Nissen fundoplication) in 5%, duodenal dilation in 22%, diminished peristalsis in 20%, delayed emptying in 12%, and luminal narrowing in 7%. Late duodenal dysmotility resulting in mega-duodenum will require tapering duodenoplasty in 4% of patients. The operative and late mortality rates are largely due to complex congenital heart anomalies. The overall long-term survival is 86%.

Laparoscopic approaches to repair of duodenal webs and atresia have been described with similar operative time, improved cosmesis, minimal morbidity, and potentially quicker return of bowel function.

Jejunoileal Atresia

Jejunoileal atresia (JIA) is estimated at an incidence of 1 to 3 per 10,000 live births. Among cases of jejunoileal obstruction, atresia occurs in 95%, while stenosis occurs in 5%. The etiology of JIA differs from that of duodenal atresia. JIA commonly result from ischemic insults such as volvulus (27%), malrotation (19%), gastroschisis (17%), and intussusception (2%) that may occur in utero. There appears to be equal distribution among males and females. Maternal smoking and cocaine use during pregnancy have been implicated in JIA. Associated anomalies are rare; however, conditions such as cystic fibrosis, gastroschisis, and malrotation have been noted in about 10% of patients.

Inheritable causes for JIA have been published. A rare entity, hereditary multiple intestinal atresia (HMIA), is an autosomal recessive disorder described in French Canadians. HMIA has been associated with combined immunodeficiency, and is almost always fatal.

The diagnosis of bowel obstruction is made with assistance of fetal ultrasound in 29% of cases via identification of enlarged loops of bowel in conjunction with polyhydramnios, although about 50% of such positive scans are false-positive studies. Postnatally, the diagnosis can be made by plain radiography when a large loop of dilated, air-filled bowel is noted (Fig. 9-22). If such very large, dilated loops are noted, further preoperative diagnostic studies are not mandatory to confirm JIA. A water-soluble contrast enema is done to rule out colonic pathology, which is often missed during operative
exploration. This often demonstrates a diminutive and unused colon. Peritoneal calcification is noted in 12% of patients, indicating prior in utero perforation and saponification of fat from pancreatic enzymes in the extruded meconium. The presence of calcifications is suggestive of meconium peritonitis, which is associated with an in-utero bowel perforation that may be due to one of many causes, sometimes resulting in JIA.

**FIGURE 9-22** Abdominal x-ray showing dilated bowel loops, suggestive of bowel obstruction. Black arrow points to a calcified lesion within the abdominal cavity, indication of meconium peritonitis.

Different types of JIA are observed. The four main types are as follows. Type I (membranous) occurs in 23%, type II (fibrous cord) in 27% (*Fig. 9-23*), and type IIIa (mesenteric gap) in 18%. Type IIIb, the “apple-peel” or
“Christmas-tree” deformity, occurs in approximately 10% of cases. This type is associated with atresia near the ligament of Treitz, and precarious, retrograde blood supply from the ileocolic, middle colic, or right colic arterial distribution to the distal bowel. The deformity is associated with a longer length of hospital stay, multiple operations, and decreased survival compared to other atresias. Type IV is associated with multiple atresias and is observed in 24% of cases.

**FIGURE 9-23** Intestinal atresia. Arrows point to multiple atretic segments; likely type 2 atresia.

Clinical presentation of JIA may consist of a newborn with bilious vomiting, abdominal distention, and a history of prenatally visualized dilated loops or maternal polyhydramnios. Presenting signs may differ based on the level of the atretic segment or segments. In proximal atresias, newborns may not demonstrate abdominal distention and may have in-utero polyhydramnios. In contrast, with distal atresias newborns may manifest abdominal distention and failure to pass meconium. As long as radiologic findings exclude malrotation with volvulus, intravenous fluids may be administered, a nasogastric tube placed, and a timely, but not emergent, operation performed. Over 50% of patients with JIA require parenteral
nutrition. Central venous access should be established before or at the time of operation in anticipation of prolonged parenteral nutrition support.

Operative approach to JIA can be either open or laparoscopic. In the open approach, the bowel is eviscerated and any twists reduced via a supraumbilical transverse incision. Trans-umbilical approaches with and without laparoscopy have also been described for simple intestinal atresia, with repair performed following evisceration through the umbilical incision. Examination for malrotation must be deliberate so that this anomaly is not missed. With terminal ileal or colonic atresia, a seromuscular biopsy of the rectum can be performed just proximal to the peritoneal reflection to evaluate for Hirschsprung disease (HD). As 6% to 20% of newborns may have more than one atresia, it is important to interrogate the distal bowel for any other atretic segments. To do so, a 10 Fr catheter is placed into the small bowel distal to the atresia and saline gently infused until it reaches the terminal ileum. If no contrast enema was performed, saline is infused to the rectum to rule out the presence of another atretic segment of bowel.

The dilated proximal segment should be resected to a reasonable caliber of bowel to prevent subsequent anastomotic dysfunction, since the massively dilated proximal bowel has abnormal smooth muscle and ineffective peristalsis (Fig. 9-24). This entails resection of the most bulbous end of the proximal bowel, placement of a 20 Fr catheter into the proximal end, and resection of the excess caliber of bowel using suture or stapling techniques. A discrepancy in caliber between the proximal and distal bowel will still be present, and therefore a proximal end to distal oblique anastomosis is performed by resecting the proximal bowel at a 90-degree angle and the distal bowel at an oblique angle. An antimesenteric incision on the distal bowel can equalize the caliber. The bowel anastomosis is very similar to a vascular anastomosis and is performed with one layer of interrupted 5-0 Vicryl suture starting at the mesenteric border. The closure is continued three-fourths of the way around, at which point the closure is started in the other direction. It is critical that the final sutures are not placed near the antimesenteric area of the bowel, as this might compromise the distal lumen. If resection would compromise bowel length, an antimesenteric tapering enteroplasty of the proximal bowel can reduce the lumen size.
In patients with compromised blood supply or in the setting of meconium ileus or meconium peritonitis, it may be reasonable to perform a double-barrel enterostomy instead of an anastomosis.

If an apple-peel deformity is noted with tenuous blood supply to the distal bowel, an anastomosis may be performed while being careful to avoid a twist in the distal bowel mesentery. Alternatively, forming a proximal enterostomy while leaving the distal bowel intact is a reasonable option.

In patients with gastroschisis, the thickened bowel often precludes resection and anastomosis. In this case, the bowel is reduced and the atresia addressed approximately 3 weeks later, when the bowel inflammation and thickening have resolved. Patients with meconium ileus and all others with volvulus and atresia should have a workup for cystic fibrosis. Suction rectal biopsy to evaluate for HD should be performed in patients with colonic atresia and those with volvulus and atresia in the terminal ileum.

Postoperative complications include adhesive bowel obstruction (24%), functional obstruction at the site of the anastomosis (9%), and the occasional anastomotic leak or stricture (4%). There is a reported higher incidence of anastomotic leak in those patients diagnosed with HD and JIA. Prolonged
dysfunction of the proximal dilated intestine is quite common, and days to weeks may pass before enteral feeds are tolerated. Evaluation for bowel obstruction by contrast enema or UGI contrast study should be performed after a few weeks if enteral feeds are not tolerated. Typically, a contrast study demonstrates a widely patent anastomosis. If the anastomosis is patent and feeding intolerance persists, a revision of the anastomosis with resection of additional bowel and/or performance of an enteroplasty to reduce the proximal bowel caliber may be required. Anastomotic complications, such as a leak, may be indicated by persistent pneumoperitoneum or, more commonly, by development of a fistula. If sepsis is present, operative intervention is required. If not, antibiotic treatment and parenteral nutrition typically allow resolution of the leak and fistula. Rarely, a leak is present with an associated abscess which requires drain placement.

Bacterial overgrowth is a long-term complication that manifests as vomiting, diarrhea, and abdominal distension. Bacterial overgrowth is treated with antibiotics with aerobic and anaerobic coverage, and if acute and severe, a short course of broad-spectrum intravenous antibiotics. Occasionally, resection of a dilated segment or enteroplasty will be required to resolve recurrent bacterial overgrowth. Chronic blood loss from the anastomosis or an adjacent ulcer can occur many years after the initial operation. Although the exact etiology is unclear, this is thought to be due to ischemia at the anastomosis. Resection and revision of the anastomosis is curative, although the ulcer may be near but not at the anastomosis and can therefore easily be missed.

Survival has increased in recent years to approximately 85% to 90%. Even those with an apple-peel deformity are expected to survive and, despite early morbidity, will likely have an excellent long-term outcome. The perioperative mortality of approximately 1% is mainly related to associated anomalies such as congenital heart disease and sepsis. The long-term causes of death are mainly related to the SBS observed in 25% of patients with JIA. Parenteral nutrition has markedly enhanced outcome in patients with atresia. However, those patients with short bowel syndrome and long-term dependency on parenteral nutrition may endure numerous episodes of catheter sepsis, likely related to translocation of enteric organisms. Vitamin deficiencies can also occur and levels should be evaluated regularly. In addition, cholestasis from parenteral nutrition with associated liver failure is a potentially lethal complication in infants that is not as prevalent in adults. Improved bowel
lengthening procedures such as the STEP procedure and improved medical care have enhanced the lifespan of patients with SBS. Although much improved, liver and small bowel transplantation have not yet had a consistent impact upon outcome in SBS patients.

**Meconium Ileus**

Meconium ileus is present in approximately 10% to 20% of newborns with cystic fibrosis. The reported incidence of meconium ileus is 1 in 3000 live births. Approximately 80% of newborns with meconium ileus will have underlying cystic fibrosis. The presence of thick, tenacious meconium in the intestines resulting from secretion of viscous intestinal mucus, an abnormal concentrating process in the proximal bowel, and impaired pancreatic enzyme secretion can result in a bowel obstruction in patients with meconium ileus. An adolescent variant of meconium ileus, distal intestinal obstruction syndrome (DIOS), is seen in 9% of patients with cystic fibrosis who develop thickened succus, which can result in bowel obstruction.

Meconium ileus is divided into simple and complex. The simple form consists of obstruction of the terminal ileum and occurs in 55% of cases. In the complex form, meconium-filled bowel may twist and produce a volvulus, resulting in ischemic necrosis with associated perforation (19%) and/or atresia (48%). Perforation, with intraperitoneal dissemination of sterile meconium, may lead to isolated regions of calcification (meconium peritonitis) or even the development of a large meconium-containing pseudocyst (19%). Extraintestinal anomalies are uncommon with meconium ileus, other than its association with cystic fibrosis and related sequelae.

Clinical presentation of the newborn with meconium ileus is similar to that of distal bowel obstruction, with emesis (which may be bilious), intolerance of feeds, and failure to pass meconium in the first 24 to 48 hours of life. The hallmark of the newborn with meconium ileus is abdominal distention at birth, with multiple doughy loops of dilated bowel noted on palpation (Fig. 9-25). A nasogastric tube is inserted for gastric decompression.
FIGURE 9-25 Distended abdomen with dilated loops visible and palpable on examination.

UGI series is not the primary investigation of choice for meconium ileus because the contrast administered from above may not progress beyond the point of inspissated meconium and, depending on contrast progression, may provide minimal information. However, importantly, UGI with a water-soluble contrast agent may help rule out malrotation and volvulus as a cause
of bilious emesis.

For simple meconium ileus, a contrast enema can be both diagnostic and therapeutic (Fig. 9-26). Gastrograffin, hypaque, or Conray may be used to perform the study; the osmolarity of the contrast agent does not appear to be of importance. A small, unused microcolon is noted with thick, inspissated meconium in the terminal ileum. The distal small bowel must be filled or the study is unlikely to be therapeutic. The hypertonicity of the gastrograffin likely draws fluid into the bowel lumen, which aids in mobilizing the meconium. As such, the newborn undergoing such studies must be kept warm and well hydrated during and following the study: typical fluid requirements are greater than the normal neonate, and attention must be paid to urine output. Contrast studies are effective at relieving the obstruction in 40% to 60% of patients with simple meconium ileus. Additional enemas may be performed over the ensuing days as long as progress is made with meconium being mobilized and evacuated, and complications such as perforation, worsening abdominal distension, or sepsis, are not encountered.
Additional investigations such as sweat chloride test and suction rectal biopsy are needed in patients to diagnose underlying cystic fibrosis or HD in patients with findings consistent with meconium ileus. A sweat chloride test may be inconclusive if performed in the first 3 weeks of life due to inadequate sweat production in newborns; therefore, a repeat sweat test and
confirmatory cytogenetics are useful, as up to 21% of patients with meconium ileus will not have laboratory or other clinical evidence of cystic fibrosis. Newborn screening with immunoreactive trypsinogen and CFTR gene mutations can increase the sensitivity. Trypsinogen, the precursor to trypsin, is elevated in patients with cystic fibrosis.

If contrast enemas are unsuccessful, operative intervention primarily consists of evacuation of the obstructing meconium from the terminal ileum (Fig. 9-27). An enterotomy is performed in the dilated ileum just proximal to the change in lumen caliber, providing access to evacuation of meconium by external massage and irrigation of the bowel via an 8 to 10 Fr catheter with warm saline, 2% to 4% N-acetylcysteine, or gastrograffin. Thick meconium is evacuated through the enterotomy or flushed into the colon. The appendix can be removed and a catheter placed into the base of the appendix to flush the terminal ileum and colon. A contained perforation may sometimes be seen at the time of laparotomy. If the meconium cannot be successfully evacuated, the bowel has been compromised, or an atretic or stenotic segment is identified, the involved segment of ileum should be resected. One option is to perform a simple end-to-end anastomosis after evacuation of distal meconium, because the long-term surgical morbidity is lower than with an enterostomy. If peritonitis, bowel compromise, concern for bowel dysfunction, or concurrent medical problems make an anastomosis tenuous, formation of an ileostomy with an adjacent mucous fistula is an alternative, with plans for establishing bowel continuity in 4 to 6 weeks. A primary anastomosis decreases the hospital length of stay and avoids a second laparotomy; however, nearly 31% require reoperation for postoperative bowel obstruction from adhesions and strictures in this population.
FIGURE 9-27  Meconium ileus with removal of meconium ball (A) and evacuation of inspissated meconium (B).

Meconium ascites or a meconium pseudocyst may be the result if an intra-uterine perforation has occurred (Fig. 9-28). The goal of surgery in the setting of meconium ascites or a pseudocyst is to identify the site of perforation and to ensure bowel continuity. In many cases, an ileostomy is required. The rind that forms the pseudocyst is left on the bowel, thus avoiding injury. In general, careful blunt dissection allows separation of the loops of bowel until the entire small bowel is mobilized.
Recent improvements in perioperative care and management of patients with cystic fibrosis have resulted in nearly 100% survival rates. Dilute 10% N-acetylcysteine may be administered through the nasogastric tube after resolution of the obstruction to prevent recurrent inspissated secretions. Anastomotic leak is unusual. Postoperative care is specifically aimed at treatment of pulmonary problems, with excellent pulmonary hygiene and administration of antibiotics. Parenteral nutrition is administered until enteral feeding of a predigested, low long-chain fatty acid formula, such as Pregestimil, is tolerated. Oral pancreatic enzyme administration is necessary with the initiation of feeding. Closure of the ileostomy, if present, is often accompanied by bowel dysfunction. One option to determine if the patient is ready for ostomy closure is refeeding of the ileostomy output via the mucus fistula. Refeeding the distal limb has been shown to be safe even in premature neonates while decreasing parenteral nutrition requirements, preventing disuse atrophy, and facilitating subsequent reanastomosis.

Long-term complications are related to the cystic fibrosis and its treatment. Early diagnosis of cystic fibrosis and treatment using enzymes in
patients with meconium ileus has been shown to improve long-term growth and prevent malnutrition. In matched cohorts of patients with cystic fibrosis with and without meconium ileus, there is no difference in long-term outcomes regarding nutritional status and hepatobiliary and pulmonary function.

DIOS may be associated with inadequate enzyme replacement or fluid intake and is usually successfully managed with administration of gastrograffin as an enema or orally. Colonic strictures, known as CF fibrosing colonopathy, can occur in association with high-dose enzyme administration and require operative colonic resection. Rectal prolapse can occur between 1 to 3 years of age, and generally resolves with oral enzyme therapy or rectal cautery and sclerotherapy. Intussusception and biliary disease can also occur in patients with cystic fibrosis.

**Meconium Plug Syndrome**

Meconium plug syndrome (MPS) is reported with an incidence of 1 in 500 to 1000 live births. There have been reported associations between HD (43%) and cystic fibrosis (38%) in patients with MPS. This syndrome is common in infants of diabetic mothers (40%–50%) and is synonymous with small left colon and functional colonic obstruction in the newborn. MPS is also seen in infants with neurological depression at birth or who are hypotonic for other reasons.

The clinical presentation of MPS may be similar to meconium ileus, with abdominal distention, failure to pass meconium within the first 24 to 48 hours, and intolerance of feeds with emesis, which may be bilious. Distinguishing between these two diagnoses lies in identifying the area of intestinal obstruction. In meconium ileus, the meconium causes obstruction in the ileum, leading to dilated small bowel and a microcolon, whereas in MPS, plugs are seen in the colon which may be of normal size.

Abdominal x-ray (AXR) can be used as an initial surveyor of bowel dilatation in the search for possible etiology of bowel obstruction in the distended neonate. Although there are no particular signs on AXR, dilated bowel and the presence of stool within the colon with normal-caliber small bowel may be suggestive of MPS. Plain imaging is followed by contrast enema studies using a water-soluble contrast. As explained earlier in meconium ileus, this may be both diagnostic and therapeutic, as enema
studies may show meconium “plugs” within the colon, which may be evacuated with the enema study. Rectal irrigations should subsequently be performed until there is clinical evidence of normal bowel evacuation and improvement in the abdominal distention. Repeat enema studies may be needed. The small, contracted portion of the descending colon in these infants has led to the term neonatal small left-colon syndrome, which is associated with maternal diabetes.

Investigations for associated disease such as cystic fibrosis and HD should be undertaken in the clinically stable child. Sweat test and confirmatory tests for cystic fibrosis such as cytogenetics may be utilized. Suction rectal biopsy should be performed in these patients to rule out HD.

Surgical intervention is rarely necessary. If surgical intervention is required, it is usually secondary to underlying etiologies such as cystic fibrosis and HD.

**Small Left Colon**

Newborns with this process will present with signs and symptoms consistent with intestinal obstruction. Contrast (water-soluble) enema demonstrates a small-caliber, smooth, rounded left colon with a normal large intestine proximal to the splenic flexure. This abnormality is often found in infants with diabetic mothers. Contrast enema is often curative and the caliber of the left colon subsequently normalizes over the ensuing weeks to months.

**Hirschsprung Disease**

Hirschsprung disease (HD) refers to congenital aganglionosis of the intestine occurring in approximately 1 in 5000 live births. Neuroblasts derived from neural crest precursors normally migrate within the submucosal and intermuscular planes of the gut to the rectum by the 12th week of gestation. Arrest of this caudal migration results in ineffective peristalsis in the distal segment of bowel accompanied by increased tone. Seventy-seven percent of cases are “short segment” and located in the rectosigmoid region. Approximately 10% of cases will involve the entire colon. Rarely, extensive small bowel aganglionosis may be encountered. Approximately 50% of patients with HD are diagnosed in the newborn period and often present with
symptoms of abdominal distention, bilious vomiting, and constipation with delayed passage of meconium beyond 48 hours of life.

Unrecognized HD in infancy has been associated with a 25% to 30% mortality. Eighty percent of those patients with HD are male, and the incidence of HD among preterm newborns is rare.

AXR may be done as the initial test in a child presenting with abdominal distention and intolerance of feeds. This may show a dilated distal colon and accumulation of stool within the colon. A barium enema of the unprepared colon may demonstrate the presence of a transition zone between distal areas of intestinal spasm (aganglionic) and proximal regions of dilated bowel (ganglionic) (Fig. 9-29). However, an obvious transition zone requires time to develop and may not be present in the neonate with HD. Contrast studies may show narrowing of the colon in its entirety, an entity known as total colonic HD (Fig. 9-30). Evaluation with rectal manometry demonstrates internal sphincter contraction rather than relaxation during periods of transient rectal distention in the patient with HD. Diagnosis of HD is dependent upon the demonstration of the absence of ganglion cells with the presence of enlarged, non-myelinated nerves on rectal biopsy (Fig. 9-31). The biopsy must be obtained at least 1.5 cm. above the dentate line and may be evaluated by standard hematoxylin and eosin stain or by the Meier–Ruge stain for acetylcholinesterase, which is increased in specimens with HD. Evaluation for calretinin, which is decreased in the setting of HD, may aid in diagnosis. A suction rectal biopsy is typically performed utilizing an apparatus that entrains a piece of the mucosa and submucosa of the rectum within a guillotine-like device, which excises and captures the sample. If the suction rectal biopsy does not provide an adequate sample, then a trans-anal, full-thickness incisional biopsy should be performed in the operating room.
FIGURE 9-29 Contrast enema showing dilated proximal colon with narrowed distal segment, seen in Hirschsprung disease. Black arrow points to likely transition zone.
FIGURE 9-30 Total colonic Hirschsprung disease.
Hirschsprung’s associated enterocolitis occurs in approximately 40% of patients diagnosed with HD. Abdominal distention, fever, and diarrhea with foul-smelling, explosive, loose stools may be indicative of the presence of enterocolitis. This can result in ischemia and necrosis of the bowel above the aganglionic segment with secondary perforation. Even if bowel ischemia is not present, enterocolitis may be associated with septicemia and even death.

Medical treatment of HD once diagnosed is ineffectual and may be dangerous if enterocolitis intercedes. Standard treatment includes performance of a left lower quadrant transverse incision with initial inspection for evidence of a transition zone. Prior barium enema provides correct identification of the transition zone in 80% of patients, which may simplify intraoperative exploration. Seromuscular biopsy specimens are evaluated by frozen section for evidence of the presence of ganglion cells (Fig. 9-32). A loop colostomy is performed in the most proximal region of the normally innervated bowel. This is known as a “leveling colostomy” and allows decompression of the bowel with normalization of intestinal caliber over the ensuing 6 to 8 weeks.
FIGURE 9-32 Histological slide of a suction rectal biopsy done on a patient diagnosed with Hirschsprung disease. This is characterized by lack of ganglion cells and elevated acetyl cholinesterase (AchE) on staining. Black arrow points to a hypertrophied nerve.

Definitive surgical correction can be done with one of three common procedures. Initially the Swenson procedure was described, where the aganglionic distal segment is dissected out from its pelvic attachments and removed. The distal margin of this dissection is usually 1 to 2 cm above the dentate line. Following this, the proximal ganglionated portion and the distal anal cuff are anastomosed in an end-to-end fashion.

The Duhamel operation consists of removing the defective or aganglionated portion of the colon, but the reconnection is done via an end-to-side anastomosis. An incision is made in the rectum 1 cm proximal to the dentate line. The ganglionated segment of bowel is passed through the bloodless pre-sacral space posterior to the rectum and an anastomosis in end-to-side fashion to the incision in the rectum is performed. A stapling device is utilized to increase the size of the anastomosis between the aganglionated rectum and the ganglionated portion of bowel. This allows formation of a large “neo-rectum,” which is formed anteriorly by the aganglionated rectum and posteriorly by the normal, ganglionated bowel. The third variation, or the Soave procedure, consists of resection of the extrapelvic aganglionic segment
and creation of an aganglionated cuff by removing the mucosa of the rectum but leaving the external layers of the rectum intact. This is done to mitigate injury that could be caused by pelvic dissection in the Swenson procedure. The ganglionated segment is then pulled through this cuff and anastomosed approximately 1 to 2 cm above the dentate line.

Confidence in the accuracy of pathologic identification of normal, ganglionated bowel on frozen section is necessary before a primary endorectal pullthrough may be performed.

Mortality is rare except in the setting of enterocolitis. Postoperative complications, including anastomotic leaks, strictures, intestinal obstruction, and pelvic abscesses occur in approximately 5% of patients. Postoperative enterocolitis occurs in approximately 40% of patients regardless of the corrective procedure utilized. The incidence of enterocolitis appears to decrease with age. Overall, approximately 80% to 90% of patients followed beyond 5 years of age have normal evacuation and continence.

**Imperforate Anus**

Imperforate anus consists of an arrest of the normal descent of the rectum to the perineum. Patients may be divided into those in which the end of the rectum is above the sphincter muscles (high), partially through (intermediate), or fully through the sphincter muscles (low). From a clinical point of view, it is only necessary to distinguish between those patients with low anomalies from those that have intermediate/high anomalies. It is important to note that males frequently have high/intermediate lesions, while females have a preponderance of low malformations. A low lesion in a male may be discerned by the presence of a thin membrane covering the anus, often with visible dark meconium underneath or an anocutaneous fistula in the midline along the perineal or scrotal raphe (Fig. 9-33). In the female patient, a perineal or vaginal vestibular fistula almost always indicates the presence of a low lesion. Therefore, in both males and females, the absence of a fistula or anal membrane suggests the presence of an intermediate/high lesion.
The majority of those male patients with an intermediate/high anomaly will have an associated fistula to the genitourinary tract, typically a rectoprostatic or rectobulbar urethral fistula. The presence of the imperforate anus should be apparent at initial newborn exam, although lesions associated with a large perineal fistula or “ectopic anus” can be easily missed. If a low malformation is present, passage of meconium via a sizeable perineal or vestibular fistula may allow adequate decompression of the gastrointestinal tract. If not, symptoms of obstruction with abdominal distention and bilious vomiting may occur.

Investigational studies for imperforate anus may start with a cross-table prone film to attempt to document the distance between the distal end of the rectum and the anal opening. This is done by placing the newborn in the prone position for about 15 minutes to allow intraluminal air to travel upward. A radio-opaque marker is placed on the expected location of the anal opening, based on physical exam. These cross-table views in prone position can be utilized to assess the distance between the rectum and anal opening (Fig. 9-34). Ultrasound examination via a transperineal or infracoccygeal route has merit in identifying the distal end of the rectum facilitating
measurement between the rectum and anal dimple, although there may be considerable technician variability in conducting the exam. Other modalities such as CT or MRI are rarely used in the initial diagnostic workup for imperforate anus, but may provide additional anatomical details. MRI has been found to be superior to CT scan in terms of soft tissue anorectal assessment and avoidance of radiation.

![FIGURE 9-34](image) Invertogram with radio-opaque marker to show likely position of anal dimple externally. End of rectal pouch is designated with black arrow.

Occasionally, a low lesion may be ascertained by (i) needle aspiration of the perineum with documentation of return of meconium from the rectum within 1 to 2 cm or (ii) ultrasound evaluation of the perineum, which allows visualization of a distal rectal pouch and documentation of the distance between anal dimple and rectum. Radiologic evaluation in conjunction with physical exam will allow a low lesion to be discerned in most cases. However, if diagnosis of a low lesion cannot be established, then the newborn should be considered to have an intermediate/high anomaly.

As many as 70% of newborns with imperforate anus will have additional associated anomalies. Specifically, those malformations which constitute the
VATER or VACTERL association should be ruled out in all patients with imperforate anus. A baseline echocardiogram, spinal ultrasound, and renal ultrasound are performed. Treatment of imperforate anus depends on the level and type of lesion identified in the diagnostic studies outlined previously. If an obstructive anomaly is present, oro- or nasogastric suction should be utilized along with administration of antibiotics. Operation may await completion of diagnostic studies assessing for associated anomalies.

Sacral ratios are calculated by measuring the distance between key bony points on anteroposterior and lateral views of pelvic radiographs. The ratios provide additional information that may predict subsequent continence. Pena introduced this ratio with the concept that those children with absence of numerous sacral elements will likely have neurological aberrancies that may affect future continence even after surgical correction.

All high/intermediate lesions are initially managed with a colostomy followed by elective performance of a distal colostogram to ascertain the specific lesion and to document the presence and location of a fistula. Corrective operation is dictated by the location of the lesion (high, intermediate, or low). For high lesions, performance of a posterior sagittal anorectoplasty (PSARP) may be accomplished at 3 to 6 months of life. This procedure involves division of the perineum from the anterior border of the external sphincter muscle to the coccyx with division of all muscles of continence, including the levator ani, in the midline. The rectum and fistulous connection between the urogenital and gastrointestinal tract is identified, divided, and closed. The rectum is then approximated to the anus as the levator ani and associated muscles of continence are reconstructed in the midline around the rectum.

Innovative, minimally invasive approaches have come into play for most centers that take care of these patients. Laparoscopy-assisted anorectoplasty (LAARP) uses laparoscopic dissection to isolate the rectal pouch and to identify and ligate the fistula. External identification of the anal dimple is done using the Pena® neurostimulator. A skin opening is made, and blunt dissection is used to create a tract from the external opening through the perineum, along the projected tract of the sphincter complex. A trocar is then passed through this tract, with laparoscopic guidance, between the bellies of the pubococcygeus muscle. The neo-rectum is then pulled through this tract through the sphincter muscle complex. MRI-assisted LAARP (MRI-LAARP) is a novel method of surgical correction for patients with imperforate anus.
that utilizes MRI imaging to guide the sequential advancement of an MRI-compatible needle through the epicenter of the sphincter complex. The external sphincter complex is identified with the neurostimulator, and an MRI-compatible needle is passed through with sequential imaging of the sphincter complex to ensure that the needle is traversing through the epicenter of the complex. The laparoscopic portion of the case proceeds in a fashion similar to the LAARP. The neorectum is then pulled through the sphincter complex and anastomosed to the anal canal in the perineum (Fig. 9-35).

**FIGURE 9-35** A. Placement and advancement of the needle into the sphincter complex (depicted with red arrow). The needle appears larger than it actually is due to “blooming” artifact. B. Needle in place after advancement through the sphincter complex.

Most low malformations may be definitively repaired in the newborn period. In both males and females an anal membrane may be punctured and dilated. A perineal fistula is addressed by incision of the skin and rectum back to the posterior margin of the external sphincter with suture approximation of the rectal mucosa to the skin (cutback anoplasty) (Fig. 9-36). In the female, mobilization of a vestibular fistula requires posterior transposition of the fistula to the proper site of the anus. This latter procedure is somewhat more complex, and therefore is usually performed at 2 to 3 months of age.
The postoperative mortality of 10% to 30% is usually due to associated anomalies, mostly cardiac. Problems with rectal prolapse or anal stenosis may be observed in 5% to 10% of infants. All patients should undergo progressive anal dilatation beginning 3 weeks after operation and continuing through the following year. Patients should be followed carefully for evidence of genitourinary problems and should be placed on prophylactic antibiotics in the initial newborn period if an intermediate/high lesion is identified.

Newborns with low malformations have an excellent outlook, with fecal continence documented in 95% of patients. Constipation may, however, be a problem in those patients with low lesions and vestibular fistulas. Approximately 50% to 70% of patients with intermediate/high anomalies have good results with only occasional soiling noted. The remaining 30% to 50% of patients have fair to poor results, with varying degrees of continence. The majority of these patients may be managed with a bowel program consisting of enemas, laxatives, or constipating agents. The functional results are mostly related to the presence of sphincter muscle hypoplasia and abnormal sacral innervation which is observed in patients with...
intermediate/high anomalies.

**FURTHER READING**


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...


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ABDOMINAL WALL
INCISIONS, CLOSURES, AND MANAGEMENT OF THE ABDOMINAL WOUND

Robert E. Roses • Jon B. Morris

INCISIONS

The planning, execution, and closure of an incision have an enormous impact on the outcome of an abdominal operation. The high combined incidence of surgical site infection, wound dehiscence, and hernia formation suggests a dominant contribution of wound complications to surgical morbidity. Moreover, the quality of exposure provided by an incision influences outcome in ways that defy easy quantification. An incision must provide access to the site of abdominal pathology and allow ready extension if greater exposure is required. Indeed, the adequacy of an incision is determined above all else by the safety with which an operation can be undertaken. Nothing should compromise this, and a larger incision or even, on occasion, a second incision, should be created without hesitation if exposure is inadequate. Notwithstanding this, the incision should be executed in a fashion that anticipates a secure wound closure and interferes as little as possible with the
function and cosmesis of the abdominal wall. While the vertical midline incision remains most popular and is, perhaps, the most versatile, a variety of other incisions may have distinct advantages in specific settings.

**Choice of Incision**

Abdominal incisions can be vertically, transversely, or obliquely oriented. The avascular linea alba affords the vertical midline its superior flexibility. Indeed, when optimal exposure of the entire abdominal cavity is necessary (eg, exploration for abdominal trauma), the vertical midline incision is preferred and can be extended superiorly to the xiphoid process and inferiorly to the symphysis pubis. Resection of the xiphoid may afford even better superior exposure when needed. Alternatively, vertical incisions may be placed in a paramedian position, an approach that was previously more popular than it is today but continues to have its proponents. Transverse and oblique incisions can be placed in any of the 4 quadrants of the abdomen depending on the site of pathology. Common examples include the Kocher subcostal incision for biliary surgery, the Pfannenstiel infraumbilical incision for gynecologic surgery, and the McBurney and Rocky-Davis incisions for appendectomy. A bilateral subcostal incision affords excellent exposure of the upper abdomen. Alternatively, when superior exposure of upper abdominal organs (eg, the esophagogastric junction) is required, thoracoabdominal incisions may be used. Retroperitoneal and extraperitoneal structures (eg, the kidney, adrenal gland, and aorta) may be readily exposed through abdominal wall incisions; often obliquely oriented or curvilinear flank incisions are used. Recently, J- or L-shaped incisions have gained popularity for exposure of the upper quadrants of the abdomen and for hepatic resection in particular.

The relative merits and disadvantages of vertical versus transverse incisions remain subjects of active debate. Proponents of transverse incisions argue that they anticipate a more secure closure than with vertical incisions—a hypothesis supported by anatomic and surgical principle. The fascial fibers of the anterior abdominal wall are oriented transversely or obliquely. Transverse incisions, therefore, parallel this orientation and allow for ready reapproximation with sutures placed perpendicular to the fibers. In contrast, vertical incisions disrupt fascial fibers and must be reapproximated with sutures placed between fibers. In the latter case, the absence of an anatomic
barrier may predispose to tearing of tissues, resulting in dehiscence or hernia formation. Despite these concerns, little evidence supports a substantial benefit of transverse incisions, and proponents of vertical incisions argue that larger transverse incisions obligate division of muscle fibers with greater functional consequences and leave fewer options for remediation when hernias do develop. A number of retrospective clinical studies and a meta-analysis do suggest that transverse incisions are superior to vertical incisions with regard to long-term and short-term outcomes (eg, postoperative pain, pulmonary complications, and frequencies of incisional hernia and dehiscence).\(^1\) However, prospective data have been less definitive. One randomized controlled trial compared vertical and transverse incisions with regard to the frequency of evisceration; no significant difference in outcome was observed with either technique.\(^2\) In a more recent prospective randomized trial, no significant differences in 30-day mortality, pulmonary complications, median length of hospital stay, median time to tolerate solid food, and incisional hernia formation at 1 year were observed. More wound infections were seen with transverse incisions.\(^3\)

Controversy also persists regarding the relative advantages of midline versus paramedian incisions. The theoretical advantage of a paramedian over a midline incision is a diminished risk of wound dehiscence and incisional hernia owing to the presence of rectus muscle interposed between layers of divided fascia. In practice, when these incisions are reopened, the medial edge of the rectus muscle is frequently adherent to the anterior or posterior sheath incision and does not effectively buttress the wound. The potential advantages of the paramedian incision have also been investigated in prospective randomized trials, which have failed to demonstrate an advantage with regard to wound failure rates.\(^4\) A “lateral paramedian incision” refers to a vertical incision created several centimeters lateral to the location of the traditional paramedian incision.\(^5\) One randomized prospective study suggested a statistically significant decrease in the incidence of incisional hernia following closure of lateral paramedian incisions (0%) compared to medial paramedian incisions (14.9%) and midline incisions (6.9%).\(^6\)

In the patient who has had prior abdominal surgery, the cosmetic advantages of reentering the abdomen through a preexisting scar must be balanced against the challenges associated with dissection in a reoperative field. Close proximity of a new incision to an old one should be avoided in
order to minimize the risk of ischemic necrosis of intervening skin and fascial bridges.

**Preparation of the Surgical Site**

Prior to incision, the surgical field is prepared with antiseptic solution and draped in order to reduce skin bacterial counts and the likelihood of subsequent wound infection. Shaving prior to operation has been associated with an increased rate of surgical site infection and should, therefore, be avoided. If hair at the surgical site will interfere with accurate wound closure or precludes easy application of the sterile preparation, the use of clippers is preferred to a razor. A variety of antiseptic solutions are commonly used to prepare the skin, including povidone-iodine, alcohol, and chlorhexidine. The efficacy of povidone-iodine depends on the release of the active iodine from a carrier molecule. The solution should, therefore, be applied several minutes prior to incision to maximize its efficacy. The use of chlorhexidine gluconate has been associated with greater reductions in skin bacterial counts and lower rates of surgical site infection when compared to povidone-iodine in a number of studies and is emerging as the preferred skin antiseptic.

**Incisions: Technical Considerations**

**VERTICAL INCISIONS**

**Midline Incision.** The midline incision allows rapid access to and adequate exposure of almost every region of the abdominal cavity and retroperitoneum. It is typically associated with little blood loss and does not require transection of muscle fibers or nerves. The upper midline incision (ie, above the umbilicus) may be used to expose the esophageal hiatus, abdominal esophagus and vagus nerves, stomach, duodenum, gallbladder, pancreas, and spleen (Fig. 10-1). The lower midline incision (ie, below the umbilicus) provides exposure of lower abdominal and pelvic organs. When broad exposure is required, as in an exploration for trauma, the midline incision can be extended to the xiphoid process superiorly and to the pubic symphysis inferiorly.
In creating a midline incision, the operating surgeon and assistant apply opposing traction to the skin on both sides of the abdomen. The skin is then incised with a scalpel. Gauze pads are applied to the skin edges to tamponade bleeding cutaneous vessels, and gentle lateral traction is placed on the subcutaneous fat on both sides of the incision. The incision is then carried down to the linea alba using either electrocautery or a scalpel; the decussation of fascial fibers in the upper abdomen serves as an important landmark for the midline. The linea alba, extraperitoneal fat, and peritoneum are then divided sequentially. If exposure of both the upper and lower peritoneal cavities is required, the incision is carried around the umbilicus in a curvilinear fashion. The peritoneum itself is best divided with scissors or scalpel to avoid coagulation injury to underlying intra-abdominal organs. In addition, safe entry may be facilitated by picking up a fold of peritoneum, palpating it to ensure that no bowel has been drawn up, and sharply incising the raised fold. The falciform ligament is best avoided by entering the peritoneum to the left of the midline in the upper abdomen. To avoid injuries to the bladder, the peritoneum is entered in the upper portion of the incision. After a small opening is created in the midline, it is enlarged to accommodate 2 fingers that are then used to protect the underlying viscera as the
peritoneum is further divided along the length of the wound (Fig. 10-2).

**FIGURE 10-2** Vertical midline incision: the linea alba and peritoneum are divided.

**Paramedian Incision.** Paramedian incisions are vertical incisions placed either to the right or left of the midline on the abdominal wall. Like midline incisions, paramedian incisions obviate division of nerves and the rectus muscle and may be made in the upper or lower abdomen. Superiorly, additional access can be obtained by directing the upper portion of the incision along the costal margin toward the xiphoid process (Fig. 10-3). The anterior border of the rectus sheath is exposed and incised across the entire length of the wound. The medial aspect of the anterior rectus sheath is then dissected away from the rectus muscle to its medial edge (Fig. 10-4).
Particular care must be taken during this dissection in the upper abdomen where tendinous inscriptions that attach the rectus muscle to the anterior fascia are associated with segmental vessels. These vessels should be ligated when encountered. Once free, the rectus muscle is retracted laterally. The posterior sheath (above the arcuate line) and peritoneum are then incised to gain entry into the abdomen. During creation of a paramedian incision in the lower abdomen, the inferior epigastric vessels may be encountered and must be ligated prior to division (Fig. 10-5).

**FIGURE 10-3** Upper paramedian incision: surface markings. Additional exposure can be obtained by sloping the upper portion of the incision upward toward the xiphoid process.
FIGURE 10–4  A. Paramedian incision: dissection of the rectus muscle from the anterior rectus sheath. B. Paramedian incision in transverse section.

FIGURE 10-5 Lower paramedian incision. A. Surface markings. B. Incision of the rectus sheath. C. Retraction of the rectus abdominis muscle. D. Location of the branches of the inferior epigastric vessels that run across the lower portion of the incision. E. Peritoneum opened. F. The peritoneum is incised for the full length of the wound.

Vertical Muscle-Splitting Incision. The vertical muscle-splitting incision is made in much the same way as the traditional paramedian incision except that
the rectus muscle is split, rather than retracted laterally. This wound can be opened and closed quickly and is of particular value in reopening a previous paramedian incision where dissection of the rectus muscle away from the rectus sheath can be difficult. Longer incisions should be avoided, however, because they result in significantly more bleeding and sacrifice of nerves that may lead to muscle atrophy and weakening of the corresponding area of the abdominal wall.

**TRANSVERSE AND OBLIQUE INCISIONS**

Transverse and oblique incisions generally follow Langer’s lines of tension and allow a more cosmetic closure than do vertical incisions. Importantly, the rectus muscle has a segmental innervation derived from intercostal nerves that enter the rectus sheath laterally. Transverse or slightly oblique incisions through the rectus largely spare these nerves. Provided that the anterior and posterior fascia is closed, the rectus muscle can be divided transversely without significantly compromising the integrity of abdominal wall. Although properly placed transverse incisions can provide exposure of specific organs, they may be limiting when pathology is located in both the upper and lower abdomen.

**Kocher Subcostal Incision.** A right subcostal incision is used commonly for operations in which exposure of the gallbladder and biliary tree is necessary. The left-sided subcostal incision is used less often, mainly for splenectomy or left upper quadrant masses. A bilateral subcostal incision provides excellent exposure of the upper abdomen and can be employed for hepatic resections, liver transplantation, total gastrectomy, and anterior access to both adrenal glands.

The standard subcostal incision begins at the midline, 2 fingerbreadths below the xiphoid process, and is extended laterally and inferiorly, parallel to the costal margin (Fig. 10-6). The incision should not be placed too far superiorly because sufficient fascia must be preserved to allow a secure abdominal closure. Following incision of the rectus sheath along the plane of the skin incision, the rectus muscle is divided using electrocautery or ligatures to control branches of the superior epigastric artery. The peritoneum is then divided in the plane of the skin incision. The incision can be extended beyond the lateral aspect of the rectus muscle if necessary to facilitate
exposure.
FIGURE 10-6 Kocher incision. A. Surface markings. B. Division of the rectus and medial portions of the lateral abdominal muscles.

McBurney and Rockey-Davis Incisions. Originally described by Charles McBurney in 1894, the muscle-splitting right iliac fossa incision known as the McBurney incision is well suited for appendectomy. This incision is oriented obliquely. The McBurney incision has largely been supplanted by the Rockey-Davis incision, which is oriented transversely as opposed to obliquely, allowing for better cosmesis (Fig. 10-7).

FIGURE 10-7 Surface markings of the right iliac fossa appendectomy incisions. A. The classic McBurney incision is obliquely placed. B. The Rockey-Davis incision is transversely placed in a skin crease.

The suspected position of the appendix and the thickness of the abdominal wall influence the placement of the incision as well as its length. Examination of the anesthetized patient’s abdomen will often reveal a mass, guiding placement of the incision directly over the appendix. If no mass is palpable, the incision is centered over McBurney’s point at the junction of the middle and outer thirds of the line between the umbilicus and the anterior superior iliac spine. If the patient is obese or if extension of the incision is anticipated,
the incision should be placed obliquely, allowing ready lateral extension.

After skin and subcutaneous tissues are incised, the external oblique
aponeurosis is exposed and divided parallel to the direction of its fibers to
reveal the underlying internal oblique muscle. At a point adjacent to the
lateral border of the rectus sheath, a small incision is made in the internal
oblique muscle, which is similarly opened in the direction of its fibers. Once
the underlying transversalis muscle is exposed, it is split to reveal the
transversalis fascia and peritoneum. These are sharply divided, and the
appendix and cecum are exposed (Fig. 10-8). If further exposure is necessary,
the wound can be enlarged by dividing the rectus sheath, retracting the rectus
muscle medially, and extending the peritoneal defect. If the operation
requires extension of the wound laterally, this can be accomplished through
division of the oblique muscles.

FIGURE 10-8  McBurney muscle-splitting incision. A. Division of the
external oblique aponeurosis. B. The internal oblique and transversus muscles
are split. C. The index fingers of each hand enlarge the opening. D. Incision
of the peritoneum. E. Exposure of the appendix.
**Pfannenstiel Incision.** The Pfannenstiel incision is used frequently for gynecologic operations and for access to the retropubic space (eg, for extraperitoneal retropubic prostatectomy). The skin incision is placed in the interspinous crease above the symphysis pubis. The anterior rectus sheath is exposed and divided transversely. The superior and inferior leaflets of the divided sheath are dissected from the underlying rectus muscles superiorly to the umbilicus and inferiorly to the pubic symphysis. The recti are retracted laterally and the peritoneum is opened vertically in the midline. At the inferior aspect of the wound, the bladder is protected to avoid injury (Fig. 10-9). An advantage of this incision is that it affords a cosmetic closure because it is placed in a skin crease at the level of the belt line; however, exposure may be somewhat limited.

ABDOMINOTHORACIC INCISIONS

The thoracoabdominal incision provides enhanced exposure of upper abdominal organs. A left thoracoabdominal incision is useful for access to the left hemidiaphragm, gastroesophageal junction, gastric cardia and stomach, distal pancreas and spleen, left kidney and adrenal gland, and aorta. A right thoracoabdominal incision can be used to expose the right hemidiaphragm, esophagus, liver, portal triad, inferior vena cava, right kidney, right adrenal gland, and proximal pancreas. These incisions are reserved for circumstances in which an operation cannot safely be performed through an abdominal incision, as they are theoretically associated with increased morbidity relating to a more difficult pulmonary recovery and risk of phrenic nerve injury.

The patient is placed in the “corkscrew” position on the operating room table to enhance access to both the abdominal and thoracic cavities. The abdomen is tilted approximately 45 degrees from the horizontal plane, and the thorax is oriented in full lateral position (Fig. 10-10A). Positioning is aided by the use of a bean bag. The abdominal part of the incision may consist of a midline or upper paramedian incision, which allows exploration of the abdomen. The incision is extended obliquely along the line of the eighth interspace just beneath the inferior pole of the scapula (Fig. 10-10B). Alternatively, an oblique upper abdominal incision can be used and extended directly into the thoracic portion of the incision.
FIGURE 10-10 Anterolateral thoracoabdominal incision. A. The “corkscrew” position, with the thorax in the lateral position and the abdomen at 45 degrees from the horizontal plane. Appropriate positioning on the
operating table is essential to prevent injury to the brachial plexus and minimize pressure on peripheral nerves. **B.** The abdominal incision is made first, usually a vertical midline incision that is extended into the chest through the eighth intercostal space. The pleural space is then entered. **C.** The diaphragm is usually opened in a radial fashion with an incision directed toward the esophageal or aortic hiatus. **D.** The diaphragm can alternatively be opened with a hemielliptical incision 2 to 3 cm from the lateral chest wall; this incision preserves phrenic nerve function, which is of particular importance in patients with impaired pulmonary function. (Reproduced with permission from Baker RJ, Fischer JE: *Mastery of Surgery*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.)

After entry into the peritoneal cavity through the abdominal portion of the incision, the incision is extended onto the chest wall and the latissimus dorsi and serratus anterior muscles, and then the external oblique muscle and aponeurosis are divided. The intercostal muscles of the eighth interspace are divided to allow entry into the chest cavity, and the incision is extended across the costal margin, which is divided with a scalpel. It is often useful to resect a short segment of costal cartilage to facilitate closure of the chest wall. A self-retaining rib retractor is inserted, and the intercostal space is gently spread. The diaphragm is either incised radially toward the esophageal or aortic hiatus or in a curvilinear fashion if less exposure is required. This incision also preserves phrenic nerve function and is useful for patients with pulmonary compromise.\(^\text{13}\)

At the completion of the operation, chest tubes placed in the pleural cavity are brought out through the chest or upper abdominal wall through separate incisions. The diaphragm is repaired in 2 layers using nonresorbable sutures. Pericostal sutures are placed to reapproximate the ribs. The chest muscles and abdominal wall are then closed in layers.

**L- AND J-SHAPED INCISIONS**

L- or J-shaped incisions were first described by Masatoshi Makuuchi and have gained considerable popularity for upper abdominal surgery and liver resection in particular.\(^\text{14}\) These incisions, which extend from xiphoid to the umbilicus and across the right or left hemipectus in transverse fashion, have several theoretical and real advantages. Transverse division of the rectus
muscle preserves segmental innervation and may minimized postoperative muscle atrophy. Moreover, by combining vertical and transverse components, an abdominal wall flap is created that can be retracted superiorly yielding wide exposure without division of both sides of the rectus. Optimal exposure requires appropriate placement of retractors; use of a retractor system that can be contoured to the incision (eg, the Thompson retractor system, Thompson Surgical Instruments [Traverse City, MI], or other table-based self-retaining systems) is helpful in this regard (Fig. 10-11). Appropriate alignment of the closure is facilitated by initial placement of interrupted sutures at the edge of the rectus muscle, junction of the transverse and vertical portions of the incision, and superior aspect of the vertical incision. Running closure of the fascial layers can then be undertaken. The interrupted sutures are tied prior to skin closure and reinforce the running closure.

**FIGURE 10-11** This incision begins at the xiphoid, extends to just above the umbilicus, and then extends laterally to the right. A left sided (L-shaped incision) can be created for left upper quadrant exposure. Exposure can be
RETROPERITONEAL AND EXTRAPERITONEAL INCISIONS

Retroperitoneal and extraperitoneal approaches to the abdomen have several advantages over transperitoneal exposures. Manipulation and retraction of intra-abdominal viscera are limited, and the risk of postoperative ileus is reduced. Hemorrhage is more likely to be tamponaded in the retroperitoneum than when it occurs in the peritoneal cavity. Retroperitoneal and extraperitoneal approaches can be used for operations on the kidney, ureter, adrenal gland, bladder, splenic artery and vein, vena cava, lumbar sympathetic chain, abdominal aorta, and iliac vessels, and on groin hernias.

Retroperitoneal Approach to the Lumbar Area. The retroperitoneal approach to the lumbar area is frequently used for aortic surgery, nephrectomy, lumbar sympathectomy, and ureterolithotomy. The patient is positioned with the operative side elevated 30 to 45 degrees with the knees and hips flexed. The incision extends from the lateral margin of the rectus sheath at the level of the umbilicus toward the twelfth rib for approximately 12 to 14 cm (Fig. 10-12). A portion of the twelfth rib is resected if necessary. The external oblique, internal oblique, and transversalis muscles are exposed, and divided in the direction of their fibers. The retroperitoneum is entered and the peritoneum and retroperitoneal fat are swept anteriorly. The lower pole of the kidney, ureter, and sympathetic chain are easily identified. The vena cava is exposed on the right, and the aorta is exposed on the left. If the peritoneum is unintentionally entered, it is closed immediately with continuous absorbable suture. At the conclusion of the procedure, the retroperitoneal fat and viscera fall back into place and the muscles of the abdominal wall are reapproximated in layers.
Posterior Approach to the Adrenal Glands. With the posterior approach, dissection is performed entirely in the retroperitoneal space. The patient is placed in the prone jackknife position. A curvilinear incision is made beginning on the tenth rib approximately 3 fingerbreadths lateral to the mid-line and carried inferiorly and laterally toward the iliac crest, ending...
approximately 4 fingerbreadths lateral to the midline (Fig. 10-13). The subcutaneous tissues are divided to expose the posterior layer of the lumbodorsal fascia. This fascia and the fibers of the latissimus dorsi muscle, which originate from it, are divided. The erector spinae muscle is exposed and retracted medially to uncover the twelfth rib and the middle layer of the lumbodorsal fascia. The attachments of the erector spinae to the twelfth rib are divided with electrocautery; the vessels and nerves that penetrate the fascia are secured with clamps and ligated. The twelfth rib is then resected. Gerota’s fascia is exposed by incising the lumbodorsal fascia along the lateral margin of the quadratus lumborum muscle. The intercostal neurovascular bundle should now become visible directly below the bed of the resected twelfth rib. The intercostal vessels are clamped, divided, and ligated, and the intercostal nerve is retracted downward. The posterior fibers of the diaphragm are identified and divided where they insert on the periosteum of the twelfth rib. The lower margin of the lung will enter the field with hyperinflation. If the pleura is inadvertently injured, the resulting pneumothorax is handled at closure by insertion of a large-bore rubber catheter into the pleural cavity that is brought out through the wound. After closure of the fascial fibers around the catheter, the lung is hyperinflated evacuating all air from the pleural space, and the catheter is briskly removed.
FIGURE 10-13 The posterior approach to the kidney and adrenal. A. J-shaped incision over the tenth to twelfth ribs, extending inferiorly 6 to 10 cm below the twelfth rib. B. Resection of the twelfth rib facilitates exposure. C. The diaphragmatic attachment to the twelfth rib is taken down, with care taken not to enter the pleura. If the pleura is opened, the wound closure is performed over a pleural suction catheter, which is removed with simultaneous positive airway pressure by the anesthetist as the skin is being closed. (Reproduced with permission from Baker RJ, Fischer JE: Mastery of Surgery, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.)

**Retroperitoneal Approach to the Iliac Fossa.** The retroperitoneal approach to the iliac fossa provides access to the bladder, distal ureter, and common, internal, and external iliac vessels. It is often employed for surgery on the
iliac arteries and for kidney transplantation. It may also be used to drain psoas or retrocecal abscesses and to resect retroperitoneal tumors. The skin incision is oriented obliquely and extends from approximately 2 cm above the anterosuperior iliac spine to a point just lateral to the pubic symphysis (Fig. 10-14). The incision can also be extended superiorly as far as the costal margin if necessary. The external oblique, internal oblique, and transversus abdominis muscles are divided in line with the skin incision. The retroperitoneum is entered and the retroperitoneal fat and peritoneum are swept superomedially. If the peritoneum is inadvertently entered, it is closed immediately. At the conclusion of the procedure, the retroperitoneal fat and viscera fall back into place and the muscles of the abdominal wall are reapproximated in layers.

**FIGURE 10-14** Right lower quadrant extraperitoneal approach to the iliac vessels, ureter, and bladder. **A.** The skin incision may be shorter than depicted in thinner patients or if an abscess is to be drained. **B.** Peritoneum is retracted medially by blunt dissection, which exposes the psoas muscle and gonadal artery and vein, shown anterior to the ureter. (Reproduced with permission from Baker RJ, Fischer JE: *Mastery of Surgery*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.)
LAPAROSCOPIC INCISIONS

As with open abdominal incisions, laparoscopic access must allow optimal exposure without unnecessarily compromising abdominal wall function or cosmesis. Laparoscopic incisions may be placed anywhere on the abdominal wall. When appropriate, laparoscopic incisions should allow for ready extension should conversion to open operation become necessary. Additionally, laparoscopic access may be combined with small open incisions that accommodate appliances through which a hand can be inserted into the peritoneal cavity without the loss of pneumoperitoneum. Such hand-assisted laparoscopic approaches are frequently associated with shorter operative times than are purely laparoscopic approaches and may have particular advantages for operations in which a larger incision is necessary to remove the surgical specimen (eg, laparoscopic colectomy) and more complex procedures. The initial step of any laparoscopic procedure is the establishment of pneumoperitoneum. This can be achieved using an open or closed technique. Access is most often obtained at a site just above or below the umbilicus—the thinnest portion of the abdominal wall and a central location from which all quadrants of the abdominal cavity can be visualized. Other sites are preferable in specific circumstances (eg, left upper quadrant access in a patient with a previous midline incision).

INITIAL ACCESS

The open approach involves the creation of a small incision, generally 1.5 cm, through which the abdominal fascia is grasped with straight clamps and elevated toward the wound. Exposure of the fascia is often enhanced with the use of S-shaped retractors. The fascia and then peritoneum are divided under direct vision. Abdominal entry is confirmed by digital palpation. Heavy stay sutures are then placed in each fascial edge and are lifted up while a blunt-tipped (Hasson) obturator and cannula are inserted through the opening in the abdominal wall. The stay sutures are then wrapped around the struts on the cannula to secure it in position. Insufflation tubing is then attached to the cannula and the obturator is withdrawn. Carbon dioxide (CO₂) is insufflated into the abdomen to a pressure of 12 to 15 mm Hg.

The closed technique involves the passage of a sharp needle (Veress needle—a spring-loaded needle with an inner blunt tip) through the
abdominal wall into the abdominal cavity. A small skin incision is made in the skin through which the needle is inserted, generally at an angle of 45 degrees to the abdominal wall; an angle of 90 degrees is sometimes necessary in the obese patient. As the needle passes through the fascia and then the peritoneum, a sensation of overcoming resistance is appreciated, often reinforced by an audible *click* as the blunt tip of the needle springs forward. A 10-mL syringe containing 5 mL of saline is attached to the end of the needle and is aspirated. If enteric contents, blood, or urine is not aspirated, the saline is instilled through the needle. If the needle is appropriately placed in the peritoneal cavity, saline should pass through the needle without resistance and the meniscus should descend down the hub of the needle when the syringe is detached (the so-called *drop test*); free descent of the meniscus sometimes requires manual elevation of the abdominal wall. The presence of significant resistance in the syringe or failure of the meniscus to descend usually indicates extraperitoneal placement or apposition of the needle against the underlying omentum and usually mandates replacement. Insufflation tubing is then attached to the needle. An initial pressure reading of less than 10 mm Hg further suggests appropriate placement, whereas higher pressures generally indicate extraperitoneal placement. Once satisfactory placement of the needle has been achieved, CO₂ is insufflated through the needle to a pressure of 12 to 15 mm Hg. Then needle is then removed, and a cannula and sharp trocar are inserted through an appropriately sized skin incision.

A variety of instrumentation has been developed to facilitate the closed approach. This includes expandable sheaths that are introduced over the needle and can accommodate larger ports that dilate open the fascial opening (or *radially expanding trocars*), and devices that dilate the fascial opening under direct vision (or *optical access trocars*). Such instrumentation may also obviate formal fascial closure because the resulting fascial defect is small after removal of the port.

The open approach holds the theoretical advantage of minimizing the potential for injury to intra-abdominal visceral and vascular structures. Disadvantages include the generally longer associated operative time and the occasional need for larger skin incisions, particularly in obese patients. In contrast, the closed approach is generally faster and may allow better cosmesis. Contraindications to the closed approach include the suspected or known presence of extensive intra-abdominal adhesions and pregnancy.
However, in patients who have had limited prior surgery, the closed approach may be used to gain access at a site remote from the previous surgical site. The safety of open and closed approaches has been compared in several studies. A large retrospective review of closed laparoscopy in 489,335 patients and open laparoscopy in 12,444 patients suggested higher rates of visceral and vascular injury in closed laparoscopy. Rates of visceral and vascular injury were 0.083% and 0.075% after closed laparoscopy and 0.048% and 0% after open laparoscopy, respectively (P = .002). Mortality rates after closed and open laparoscopy were not statistically different.\textsuperscript{16} Notably, this small difference was not evident in several other meta-analyses.\textsuperscript{17,18}

**PLACEMENT OF ADDITIONAL PORTS**

The approach to the placement of secondary cannulas is highly surgeon and operation specific. Some basic principles, however, should always be adhered to. These include the following: (1) all cannulas should be inserted with the aid of laparoscopic visualization; (2) cannulas must be placed far apart from one another to avoid frequent crossing of instruments (generally 10 cm or more apart); and (3) cannulas should be placed at a distance from the operative site, which maximizes range of motion at the cannula site and minimizes operator discomfort (approximately 15 cm). In addition, skin incisions, while often small, should never compromise easy passage of trocars through the abdominal fascia. Undue resistance at the level of the skin can undermine the surgeon’s control of the trocar as it passes through the peritoneum and lead to injury of underlying viscera or vascular structures.

**CLOSURE OF ABDOMINAL INCISIONS**

As noted above, wound complications make a dominant contribution to surgical morbidity. Indeed, wound infection is the most common early complication and incisional hernia is the most common long-term complication of open abdominal surgery. Multiple factors contribute to the incidence of wound failure including diabetes mellitus, malnutrition, obesity, and corticosteroid use. Surgical technique, too, appears to influence rates of wound failure; however, there has been little consensus regarding the optimal approach to closure. An evolving literature focuses on the relative merits of
Closure of the Fascia

The abdomen can be closed in multiple layers or en mass. The former technique reconstructs the anterior and posterior aponeurotic sheaths separately, with the posterior layer generally incorporating the peritoneum. Mass closure involves a single-layer closure of all layers and may or may not include the peritoneum. Numerous clinical trials have compared multiple layered to mass abdominal closure. Some studies have shown an increased incidence of dehiscence and incisional hernia formation with multiple layered closure, while other studies show no difference in the incidences of these complications. Given the shorter time required to close the fascial layers en mass, this method is generally preferred.

The relative advantages of resorbable versus nonresorbable sutures for use in closing the fascia have long been debated. Opponents of closure with nonresorbable suture invoke higher rates of suture sinus formation and increased postoperative pain; the incidences of these complications have been estimated at 8% and 17%, respectively. In contrast, it has been suggested that closure with resorbable suture may lead to increased incidences of dehiscence and hernia formation due to an intrinsic loss of tensile strength during the postoperative period. While these complications are certainly seen with increased frequency when absorbable catgut suture is used, the literature has not consistently borne out an association between wound failure and the use of resorbable sutures such as polyglycolic acid (Dexon), polyglactic acid (Vicryl), polydioxanone (PDS), and polyglyconate (Maxon). In particular, several studies comparing permanent (Prolene, Ethicon, or nylon) versus slowly absorbable sutures (PDS and Maxon) have failed to demonstrate any advantage to the use of nonresorbable suture. There may be some advantage to the use of slowly resorbable compared to rapidly resorbable suture; one study demonstrated a significant decrease in the rate of hernia formation when slowly resorbable sutures (PDS and Maxon) were used compared to more rapidly resorbable sutures (catgut, Dexon, and Vicryl) \( (P = .009) \). Nonresorbable sutures do appear to be associated with a higher incidence of suture sinus formation. This association may be greatest...
with multifilament permanent sutures, which may abet bacterial ingrowth and infection.\textsuperscript{23,26} Table 10-1 shows the rates of resorption for different suture materials.\textsuperscript{35}

<table>
<thead>
<tr>
<th>Suture Material</th>
<th>Time Until Total Resorption (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly resorbable</td>
<td></td>
</tr>
<tr>
<td>Catgut</td>
<td>15</td>
</tr>
<tr>
<td>Chromic catgut</td>
<td>90</td>
</tr>
<tr>
<td>Polyglycolic acid (Dexon)</td>
<td>20</td>
</tr>
<tr>
<td>Polyglactin 910 (Vicryl)</td>
<td>60-90</td>
</tr>
<tr>
<td>Slowly resorbable</td>
<td></td>
</tr>
<tr>
<td>Polydioxanone (PDS)</td>
<td>180</td>
</tr>
<tr>
<td>Polyglyconate (Maxon)</td>
<td>180</td>
</tr>
<tr>
<td>Nonresorbable</td>
<td></td>
</tr>
<tr>
<td>Nylon (Nurulon)</td>
<td>—</td>
</tr>
<tr>
<td>Polypropylene (Prolene)</td>
<td>—</td>
</tr>
<tr>
<td>Polyethylene (Ethibond)</td>
<td>—</td>
</tr>
<tr>
<td>Polyamide (Ethilon)</td>
<td>—</td>
</tr>
</tbody>
</table>

Dexon (Davis & Geck, Wayne, NJ), Vicryl (Ethicon, Somerville, NJ), PDS (Ethicon), Maxon (Davis & Geck), Nurulon (Ethicon), Prolene (Ethicon), Ethibond (Ethicon), and Ethilon (Ethicon). Reproduced with permission from van't Riet M, Steyerberg EW, Nellensteyn J: Meta-analysis of techniques for closure of midline abdominal incisions, Br J Surg 2002 Nov;89(11):1350-1356.

It has been suggested that a continuous, running closure will result in a more durable wound than an interrupted closure. The former may allow the more even distribution of tension across the suture line with less resultant tissue strangulation and wound disruption. The obvious disadvantage of a continuous closure is its dependence on a single suture. The majority of studies comparing interrupted and continuous closure, however, demonstrate similar incidences of wound dehiscence, incisional hernia, wound infection, wound pain, and suture sinus formation.\textsuperscript{27,29-32} One recent randomized trial
compared interrupted and continuous closure with resorbable suture. No significant difference in the rates of incisional hernia, dehiscence, or wound infection were observed. A more recent randomized study indicated that smaller (5 mm every 5 mm) compared to larger fascial bites (1 cm every 1 cm) resulted in fewer hernias.

In summary, an evidence-based approach to laparotomy closure narrowly favors the use of nonresorbable or slowly resorbable sutures in order to minimize the risk of hernia formation. The latter is preferred because of the lower associated risk of suture sinus formation and decreased postoperative pain. A running closure is associated with either an equivalent or lower risk of hernia formation and, given the ease and speed with which it can be performed, is to be preferred. Importantly, undue tension should not be placed on the running closure to avoid strangulation of the fascia.

**Technique of Mass Closure of the Abdomen**

When closing a midline laparotomy incision, 2 size #0 looped or size #1 nonlooped slowly resorbable monofilament sutures are generally used. One suture is anchored at the upper extent and one at the lower extent of the wound. A malleable retractor can be used to protect the underlying viscera while the fascia is closed. The suture is passed in a continuous or interrupted manner, taking full-thickness bites of the linea alba fascia incorporating both the anterior and posterior rectus aponeuroses (Fig. 10-15). An assistant holds steady tensions on the suture while the closure progresses. Repetitive relaxation and application of tension of the suture are avoided to limit injury to the fascia. Likewise, it is unnecessary and probably counterproductive to overly tighten the suture as closure progresses, as this may lead to fascial necrosis. This point has been illustrated in a study associating evisceration and hernia formation with a lower suture length–to–wound length ratio. The 2 sutures are run toward one another and then tied together in the center of the wound.
Skin Closure

A number of skin closure techniques can be used following clean (class I) or clean-contaminated (class II) operations; these include interrupted suture, subcuticular suture, stapled, and adhesive glue. Three randomized controlled studies have compared stapled to subcuticular suture closures. Both techniques are associated with equivalent rates of wound infection. Two of the studies suggested that subcuticular suture closure is associated with less postoperative pain than is stapled closure. Two studies also demonstrated a superior cosmetic result early following suture closure; however, this difference was insignificant by 6 months after operation.

Glues are used with increasing frequency for skin closure. Advantages of glues include ease and rapidity of application and simplification of wound care; generally, no additional dressing is required. Closure with glues has been compared to traditional skin closure methods in several clinical trials.
Wound durability appears to be comparable, although there are conflicting data on cosmesis and postoperative pain. If the surgical site is contaminated (class III or class IV wound), the skin should be left open to heal by secondary intention or by delayed primary skin closure.

**Retention Sutures**

The incidence of fascial dehiscence after major abdominal operations is 1% to 3% and is associated with a mortality rate of 15% to 20%. Several patient-related factors are associated with an increased risk of fascial dehiscence. These include advanced age, male sex, malnutrition, anemia, and steroid use; however, local mechanical factors and closure technique appear to have a greater influence on rate of dehiscence. Placement of drains or ostomies through the main incision compromises fascial integrity and should be avoided. Wound sepsis and increased intra-abdominal pressure, whether from ileus, bowel obstruction, atelectasis, or after hernia repair, also compromise the integrity of a fascial closure. Indications for prophylactic placement of retention sutures at initial operation remain controversial. The purpose of retention sutures in this setting is to relieve tension along the suture line in order to prevent significant wound disruption and evisceration in the patient at high risk.

There has been only 1 randomized trial comparing closure with and without retention suture placement; Hubbard and associates could not identify a benefit of retention suture closure over standard mass closure of the abdominal wall. The potential disadvantages of retention sutures, however, are well known and include entrapment of underlying viscera, increased postoperative pain, poor cosmesis, and leakage of intraperitoneal fluid through the wound. Some surgeons advocate primary closure with retention sutures in selected circumstances. In a retrospective study of midline abdominal wound dehiscence, Makela and colleagues identified preoperative variables that are significantly associated with fascial disruption; these include hypoalbuminemia, anemia, malnutrition, chronic pulmonary disease, and emergent operation. For patients with 3 or more of these preoperative risk factors, this group recommended internal retention suture closure.

When employed, retention sutures are placed across the wound prior to
formal fascial closure. Interrupted permanent monofilament sutures are passed through skin and fascia approximately 2 cm from the wound margin at intervals of several centimeters. Placement is facilitated by the use of a long cutting needle. It may be advantageous to omit the peritoneum from the retention closure in order to protect underlying viscera from injury or entrapment. After conventional closure of the fascia, the sutures are threaded through rubber tubing bolsters or commercially available plastic bolster devices and tied at the skin level.

**Mesh and Biologic Implant Placement**

Placement of a mesh underlay represents an alternative approach to the prophylactic placement of retention sutures for the *at-risk* abdominal closure. In addition, the occasional operation that requires resection of a significant portion of the abdominal wall as well as transection of bowel sometimes necessitates the placement of a prosthesis in a potentially contaminated field. Interposition placement of resorbable mesh accepts a hernia that will require complex abdominal wall reconstruction to repair. Moreover, high rates of fistula formation and mesh infection have been described with resorbable as well as nonresorbable mesh in this setting. Biologic implants such as human and porcine acellular dermal allografts are an attractive alternative to meshes when faced with a difficult-to-close abdominal wall, particularly in the setting of contamination. As with resorbable meshes, underlay rather than interposition placement likely yields a much more durable result. While the use of these products in acute clinical settings has been described, there are few definitive data to guide selective application of such techniques. More complex abdominal reconstructions using component separation techniques, releasing incisions, or rectus mobilization in conjunction with mesh or biologic implants may be undertaken in appropriately selected patients when primary closure is not possible. More often, such approaches are used in a delayed fashion after development of an abdominal wall hernia.

**Closure of Laparoscopic Incisions**

The closure of laparoscopic incisions poses particular challenges.
Reapproximation of the fascia is made more challenging in the presence of small skin incisions, which limit visualization. While small fascial defects may be left open, any fascial defect 10 mm or greater in the midline or below the arcuate line should generally be closed to reduce the risk of port-site hernia formation. The use of radially expanding trocars obviates the need for formal closure in many cases, although larger midline defects still generally require suture reapproximation.

While sometimes challenging, particularly in obese patients, secure reapproximation of the fascia, usually with several interrupted sutures, can usually be achieved under direct visualization. Alternatively, a variety of instrumentation may be used to facilitate closure, usually in combination with laparoscopic visualization and maintenance of pneumoperitoneum. The Endoclose device (Tyco Healthcare, Mansfield, MA) has a sharp tip that also functions as a grasper. The tip of a suture is grasped with the device and driven through the fascia adjacent to the cannula (and fascial defect) under laparoscopic visualization. The end of the suture is left free inside the abdomen. The grasper is then placed through the fascia a second time on the opposite side of the defect, and the free end of the suture is grasped inside the abdominal cavity and pulled out through the fascia. The suture is then tied to close the defect. The Carter-Thomason System (Inlet Medical, Eden Prairie, MN) additionally includes a needle director that is inserted through the fascia instead of the cannula, which ensures that adequate fascia is obtained by directing the needle at an appropriate angle and may expedite closure.

**Temporary Closure of the Abdomen**

Despite the frequent misconception that temporary abdominal closure techniques are a recent innovation, such approaches have long been used. Indeed, Pringle reported his experience with temporary packing of hepatic injuries in 1908. In 1913, Halsted recommended interposition of a nonadherent layer between the injured liver and packs. Such an approach did fall out of favor in the period following the Second World War due to the very high observed incidences of late hemorrhage and sepsis. However, beginning in 1973 with a report by Lucas and Ledgerwood, a number of investigators suggested the feasibility and utility of temporary abdominal closure, particularly in the setting of massive traumatic injury. In 1993,
Rotondo and Schwab introduced the term damage control and outlined a 3-phase approach to the management of major abdominal injuries. The first phase consists of rapid control of hemorrhage and contamination followed by temporary abdominal closure; the second focuses on the restoration of normal body temperature, correction of coagulopathy, and optimization of ventilation; and the third involves removal of abdominal packs, definitive operation, and abdominal closure. In their initial series, Rotondo and Schwab demonstrated a marked survival advantage in patients with major vascular injury and 2 or more visceral injuries treated using the damage control approach (10 of 13 patients, 77%) compared to those definitively closed at the time of initial operation (1 of 9 patients, 11%; \( P < .02 \)). The applications of this approach have broadened with greater experience. Patients who may benefit from this damage control approach include those at risk of developing abdominal hypertension (e.g., hypothermia, coagulopathy, acidosis, large transfusion requirement) and those who require a second-look laparotomy (e.g., intestinal ischemia).

This approach has necessitated the evolution of temporary closure techniques. These range from the very simple and inexpensive (e.g., towel clip closure, running nylon suture close) to more sophisticated commercially available vacuum-assisted closure (VAC) systems. No single approach is clearly superior, and multiple techniques may have advantages in specific clinical settings. The Bogotá bag uses a large intravenous bag secured to the skin or fascia. Impermeable plastic drapes may be used alternatively in a similar fashion. This approach is fast and inexpensive, minimizes fluid losses, and is easily removed. It may be less durable than other closures; tearing of sutures through the periphery of the bag can result in evisceration. Absorbable meshes such as polyglactin 910 (Vicryl; Ethicon, Somerville, NJ) and polyglycolic acid (Dexon; Davis & Geck, Danbury, CT) can be sutured to the skin or fascia. This approach allows for a degree of flexibility as definitive closure can subsequently be undertaken without removal of the mesh. Alternatively, the mesh can serve as a bed for the elaboration of granulation tissue. If reapproximation of the fascia is not feasible or needs to be substantially delayed, a skin graft can be placed over the granulation bed. A variation on mesh closure uses the Wittman patch—a device made of 2 adherent sheets of biocompatible polymeric material. The edges of the patch are sewn to the surrounding abdominal fascia. As edema resolves, the fascial edges are gradually reapproximated by drawing the 2 sheets closer together.
and cutting away excess material.

An increasingly popular alternative to these temporary closures has been termed the open abdomen technique.\textsuperscript{63} Generally, a nonadherent barrier (eg, a towel covered with an adhesive plastic drape) is placed on top of the intra-abdominal contents, below the fascia. Jackson-Pratt drains are placed above this barrier to control drainage and maintain the integrity of an adhesive dressing placed over the entire wound and skin (\textit{Fig. 10-16}). This dressing is readily applied, inexpensive, and facilitates multiple reexplorations. Loss of abdominal domain can be limited with the additional placement of lacing across the wound, which generally involves vessel loops laced through skin staples placed along the edges of the wound that can be progressively tightened as intra-abdominal hypertension resolves. Maintenance of the open abdomen may be facilitated with the use of the commercially available abdominal VAC. The abdominal VAC is composed of a barrier enveloped in nonadherent plastic that is placed over the intra-abdominal contents below the fascial edges. A polyurethane sponge is cut to the size of the wound and placed over the barrier. The sponge is then covered with an adherent dressing. A small defect is created in the dressing, and suction tubing with an adherent appliance is applied over this defect and attached to a vacuum device. Drainage is drawn out through the sponge through the vacuum tubing and into a vacuum canister. This system is particularly useful when multiple reexplorations are anticipated. In addition, loss of abdominal domain is minimized by the negative pressure exerted on the dressing. While the use of the abdominal VAC may facilitate a more delayed definitive closure, the risk of injury to underlying viscera and fistula formation does increase with additional dressing changes.\textsuperscript{64} Therefore, in the patient who cannot undergo definitive closure after approximately 1 week, transition to a Vicryl mesh closure may be advantageous.
FIGURE 10-16 Open abdominal dressing. Top. A towel wrapped in adhesive plastic is placed between the abdominal contents and the fascia. Bottom. Jackson-Pratt drains and an impermeable dressing are applied over...
MANAGEMENT OF THE POSTOPERATIVE WOUND

Dressing the Wound

At the conclusion of a procedure, a sterile dressing is typically applied to the wound before removal of the sterile drapes. Theoretically, this dressing prevents bacterial colonization of the wound during the initial 24 to 48 hours of healing, allowing for epithelialization and the formation of coagulum. Before application of the dressing, excess antiseptic solution should be washed off with sterile saline. In general, the dressing should be secured without the use of excessive tape, which may be irritating to the skin. In most cases, the dressing can be removed within 48 hours of application. This practice is supported by studies from the 1960s documenting that exposure of clean, closed wounds to the atmosphere on postoperative day 2 is not associated with an increased incidence of infection. In many cases, after closure of a clean wound, no dressing is necessary. Indeed, in a randomized study of patients undergoing either inguinal hernia repair or high saphenous ligation, there was no significant difference in the rate of wound infection whether wounds were immediately exposed, covered with a dry gauze dressing, or covered with an occlusive film dressing.

A variety of dressing types are used in the management of surgical wounds and may have advantages in some specific clinical settings. A simple dry dressing comprised of gauze secured with sparing use of tape is generally sufficient. Wet-to-dry dressings are commonly used to dress open and contaminated wounds; mechanical debridement of the wound results from removal of dried packing material with adherent devitalized tissue. Enzymatic agents (eg, papain/urea [Accuzyme]) may be used in conjunction with wet-to-dry dressings to gently debride fibrinous exudate. In addition, application of broad-spectrum antibacterials (eg, silver sulfadiazine) may limit bacterial colonization and promote wound healing.

Recently, VAC dressings have gained great popularity for the management of open wounds. The VAC dressing has 3 components: (1) the...
VAC sponge, which is applied directly to the wound bed; (2) an occlusive dressing, which is applied over the sponge to seal it to the surrounding skin; and (3) a suction pump, which provides regulated negative pressure through the sponge. The VAC dressing has been used extensively in a variety of clinical setting and appears to promote granulation tissue formation and wound contraction. A major advantage of the VAC is the need for fewer dressing changes compared with conventional wet-to-dry dressings. As discussed earlier, the VAC has become a prominent part of the armamentarium for treating abdominal wounds that cannot be definitively closed at the time of initial operation.

**Surgical Site Infections**

Surgical site infections (SSIs) are the most common nosocomial infections in surgical patients. It has been estimated that each SSI results in 7.3 additional inpatient days and adds over $3000 to the hospital charges. The bacterial colony count at the surgical site makes a dominant contribution to the risk of wound infection; colony counts per gram of tissue of $10^5$ or greater are associated with a markedly increased risk. In the presence of a foreign body, however, a much lower count may lead to infection. Other risk factors for the development of wound infections include advanced age, obesity, diabetes mellitus, smoking, malnutrition, altered immune response, preoperative hospitalization, presence of infection at a remote body site, length of operation, and use of surgical drains.

SSIs are subdivided into 2 categories: incisional and organ/space (Table 10-2). Incisional SSIs are limited to the surgical site. They are further divided into superficial SSIs, which involve the skin and subcutaneous tissue, and deep SSIs, which involve the fascial and muscle layers. Organ/space SSIs can involve any part of the anatomy that was manipulated during the surgery except the incision.

TABLE 10-2: CRITERIA FOR DEFINING SURGICAL SITE INFECTIONS (SSIs)
Wounds can be classified by degree of contamination (Table 10-3). The risk of a postoperative SSI reflects, in part, the wound classification; however, infection rates vary widely within each classification group. Other risk-scoring systems have, therefore, been developed to better anticipate the risk of wound infections. Examples of such scoring systems are the SENIC (Study of the Efficacy of Nosocomial Infection Control) and NNIS (National Nosocomial Infection Surveillance) risk indexes. The SENIC system predicts risk associated with abdominal surgery, operations lasting longer than 2 hours, contaminated or dirty wound classifications, and operation on patients with 3 or more discharge diagnoses. The NNIS system predicts risk associated with American Society of Anesthesiologists preoperative assessment scores of greater than 2, wound classifications of contaminated or dirty, and increased duration of the operation.

**TABLE 10-3: CLASSIFICATION OF SURGICAL WOUNDS**
The organisms most commonly responsible for SSIs are Staphylococcus aureus and coagulase-negative staphylococci. After abdominal surgery, infection with enteric organisms (Escherichia coli and Enterobacter species) is also prevalent. The Centers for Disease Control and Prevention recommendations for the prevention of SSIs are summarized in Table 10-4. The use of preoperative prophylactic antibiotics in all clean-contaminated and clean cases with associated risk factors is recommended. The antibiotic of choice for most upper gastrointestinal procedures is cefazolin or a comparable first-generation cephalosporin. For colorectal surgery, metronidazole is added to this regimen. The administration of a mechanical and oral antibiotic bowel preparation has been recommended prior to colorectal surgery, although this practice has been challenged by recent meta-analyses suggesting no benefit. Preoperative intravenous antibiotics should be administered 30 to 60 minutes before the incision is made to allow the agent to reach maximal tissue concentration. In obese patients, the antibiotic should be adjusted appropriately. For long procedures, the antibiotic should be readministered after every 2 half-lives to maintain an effective serum concentration.

<table>
<thead>
<tr>
<th>Type of Wound</th>
<th>Definition</th>
<th>Risk of SSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I: Clean</td>
<td>An uninfected operative wound in which no inflammation is encountered and respiratory, alimentary, genital, or uninfected urinary tract is not entered. They are primarily closed and, if necessary, drained with close drainage.</td>
<td>1%-5%</td>
</tr>
<tr>
<td>Class II: Clean-contaminated</td>
<td>An operative wound in which the respiratory, alimentary, genital, or urinary tract is entered under controlled conditions and without unusual contamination. In particular, surgeries involving the biliary tract, appendix, vagina, and oropharynx are included in this category provided no evidence of infection or a major break in technique is encountered.</td>
<td>2%-9%</td>
</tr>
<tr>
<td>Class III: Contaminated</td>
<td>Open fresh accidental wounds. In addition, surgery with major breaks in sterile technique (eg, open cardiac massage) or gross spillage from the gastrointestinal tract and incisions in which acute, nonpurulent inflammation is encountered are included in this category.</td>
<td>3%-13%</td>
</tr>
<tr>
<td>Class IV: Dirty-infected</td>
<td>Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated visera.</td>
<td>3%-13%</td>
</tr>
</tbody>
</table>
Preoperative Factors

Preparation of the patient:
1. Identify and treat all infections remote from the surgical site and postpone elective surgery until infection has resolved.
2. Do not remove hair unless it interferes with surgery.
3. If hair is to be removed, remove immediately preoperatively using clippers.
4. Ensure good blood glucose control in diabetic patients and avoid hyperglycemia.
5. Encourage cessation of tobacco use (at least for 30 days before surgery, if possible).
6. Do not withhold blood products, as transfusion does not affect rates of SSIs.
7. Require the patient to shower or bathe with an antiseptic solution the night before surgery.
8. Remove gross contamination from the surgical site before performing antiseptic skin preparation.
9. Use an appropriate antiseptic solution for skin preparation.
10. Apply preoperative antiseptic solution for skin preparation in concentric circles moving outward toward the periphery.
11. Keep the preoperative hospital stay as short as possible.

Hand/forearm antisepsis for surgical team:
1. Keep nails short and do not wear artificial nails.
2. Perform a preoperative scrub for at least 2-3 minutes up to the elbows.
3. After performing the surgical scrub, keep the hands up and away from the body (elbows flexed) so that the water runs from the tips of fingers toward the elbows. Dry hands with a sterile towel and don a sterile gown and gloves.
4. Clean underneath each fingernail.
5. Do not wear hand or arm jewelry.

Management of infected or colonized surgical personnel:
1. Educate and encourage surgical personnel who have signs and symptoms of a transmissible infectious illness to report promptly to their supervisor and occupational health personnel.
2. Develop well-defined policies concerning patient care responsibilities when personnel have potentially transmissible infectious conditions. These policies should govern (1) responsibility of personnel in using health services and reporting illness, (2) work restrictions, and (3) clearance to resume work after an illness that required work restriction. The policies should also identify staff members who have the authority to remove personnel from duty.
3. Obtain appropriate cultures and exclude from duty surgical personnel who have draining skin lesions until infections have been ruled out or until these personnel have received adequate therapy and infection has been resolved.
4. Do not routinely exclude surgical personnel who are colonized with organisms such as *Staphylococcus aureus* or group A streptococci, unless they have been linked epidemiologically to dissemination of the organism.

Antibiotic prophylaxis:
1. Administer a prophylactic antimicrobial agent only when indicated, and select it based on its efficacy against the most common pathogens causing SSIs for a specific operation, and in accordance with published recommendations.
2. Administer by the intravenous (IV) route the initial dose of prophylactic antimicrobial agent, timed such that bactericidal concentration of the drug is established in serum and tissue when the incision is made. Maintain therapeutic levels of the agent in serum and tissues throughout the operation and for a few hours after the incision has been closed.
3. Before elective colorectal operations, in addition to the above measures, mechanically prepare the bowel by using enemas and cathartic agents. Give nonabsorbable oral antimicrobial agents in divided doses on the day before the operation.
4. For high-risk cesarean sections, administer the prophylactic antimicrobial agent immediately after the umbilical cord is clamped.
5. Do not routinely use vancomycin for prophylaxis.

Intraoperative

Ventilation:
1. Maintain positive-pressure ventilation in the operating room with respect to the corridors and adjacent area.
2. Maintain a minimum of 15 air changes per hour, of which at least 3 should be fresh air.
3. Filter all air, recirculated and fresh, through the appropriate filters per the American Institute of Architects’ recommendations.
4. Introduce all air at the ceiling and exhaust air near the floor.
5. Do not use ultraviolet radiation in the operating room.
6. Keep operating suite doors closed except as needed for passage of equipment, personnel, or patients.
7. Consider performing orthopedic implant operations in an operating suite supplied with ultraclean air.
8. Limit the number of personnel entering the operating room.

Cleaning and disinfection of environmental surfaces:
1. When visible soiling or contamination of surfaces or equipment with blood or other body fluids occurs during an operation, use an Environmental Protection Agency (EPA)-approved hospital disinfectant to clean the affected areas before the next operation.
2. Do not perform special cleaning (in addition to cleaning with routine EPA-approved hospital disinfectant) of operating rooms after contaminated or dirty operations.
3. Do not use tacky mats at the entrance to the operating room suite or individual operating rooms for infection control.
4. Wet vacuum the operating floor with an EPA-approved disinfectant after the last operation of the day or night.

Microbiological sampling:
1. Do not perform routine environmental sampling of the operating room.
The treatment for incisional SSIs includes removal of skin stitches or staples to allow drainage of any underlying collection. Antibiotics are indicated in the presence of cellulitis. The effective use of antibiotics depends on (1) appropriate coverage of the offending organisms and (2) maintenance of an adequate tissue concentration of the drug. Cefazolin or an equivalent first- or second-generation cephalosporin is appropriate for uncomplicated incisional SSI. Wound cultures are obtained in the presence of purulence and are used to guide antibiotic selection. Following abscess drainage, wounds are left open and allowed to close by secondary intention.

Deep space SSIs also require drainage. Increasingly, this is achieved by percutaneous placement of a drain under computed tomography or ultrasound guidance. Deep space infections that are not amenable to percutaneous drainage require operative drainage. Broad-spectrum antibiotics are indicated until culture data are obtained, at which point the spectrum should be narrowed to target the offending organism.
Necrotizing soft tissue infections are a heterogeneous group of clinical entities; however, several fundamental concepts govern the treatment of all. Paramount is early identification followed by operative debridement and initiation of antibiotic therapy. Patients often present early in the postoperative period (ie, within 48 hours) with incisional pain followed by the rapid onset of signs and symptoms of sepsis. While the incision may initially appear benign, more often, serous drainage is noted. Patients may also present with bullae or blebs, crepitus, cutaneous anesthesia, and cellulitis that is refractory to antibiotic therapy. Tenderness that extends beyond the borders of the apparent cellulitis suggests progression of the infection to the deeper cutaneous layers and should raise suspicion for an early necrotizing process. Importantly, fewer than 40% of patients exhibit the classic symptoms and signs described, and a high degree of suspicion should be maintained in the postoperative patient with early signs of sepsis.

In the absence of characteristic clinical features, diagnosis can be challenging. An elevated white blood cell (WBC) count (≥15,400/µL) and hyponatremia (serum sodium level <135 mmol/L) are sensitive markers for the presence of a necrotizing soft tissue infection; however, they are fairly nonspecific. Imaging studies, including plain x-ray and computed tomography, may reveal the presence of soft tissue gas, although this finding is present in a minority of cases. The reported sensitivity of magnetic resonance imaging for diagnosis of necrotizing soft tissue infection ranges from 89% to 100%, and its specificity ranges from 46% to 86%. However, the frequent presence of subcutaneous air in an early postoperative wound precludes reliable imaging in most cases, and more importantly, imaging may delay appropriate treatment.

In suspected cases, immediate surgical exploration and debridement are recommended and constitutes the most important single therapy. *Clostridium perfringens* and group A β-hemolytic streptococci are the most frequently implicated organisms, but necrotizing infections are often polymicrobial. A sample of debrided tissue should be sent for Gram stain and culture, and initial therapy should have a broad spectrum of coverage (eg, penicillin, clindamycin, and an aminoglycoside). Following initial debridement, the wound should be reexamined frequently. Any evidence of extension of the necrotizing process should prompt further debridement. Although the initial
management of all necrotizing infections is essentially the same, there are several specific clinical entities that deserve special mention, as they may require unique therapies.

**Gas Gangrene.** Gas gangrene infection after abdominal surgery results from contamination with clostridia, typically from the alimentary tract or biliary system. Patients usually present with severe wound pain often associated with fever and tachycardia. Such wounds often appear edematous and erythematous; they later become dusky and necrotic. Wound crepitus and foul-smelling watery discharge, so-called “dishwater drainage,” are characteristic. Early surgical intervention with debridement of all infected and nonviable tissue is recommended in suspected cases. Although there have been no controlled clinical trials, there is some evidence that hyperbaric oxygen is of considerable value in treating clostridial infection and reduces the mortality rate by some reports from 66% to 23%. The potential benefits of hyperbaric oxygen include improved leukocyte function and increased tissue oxygen levels, which is bactericidal for *Clostridium perfringens* and bacteriostatic for other anaerobic bacteria.

**Necrotizing Fasciitis.** This syndrome has been divided into 2 subcategories depending on the implicated organisms. Type I necrotizing fasciitis is a polymicrobial process; type II necrotizing fasciitis is caused by group A streptococci. Polymicrobial necrotizing infections are generally slowly progressive and affect the total thickness of the skin, but do not involve the deep fascia. Purulence may or may not be present. Most often, such infections are heralded by a nonspecific cellulitis around the wound that slowly extends over days. Later, the central area of the cellulitis becomes purple and then develops typical features of gangrene. These infections are referred to as Fournier gangrene when they affect the perineum. The causative organisms are usually a mixture of anaerobes, gram-negative rods, and *Enterococcus* species. Broad-spectrum antibiotics should be initiated early and then tailored pending the result of microbial cultures.

Necrotizing infections caused by group A streptococci are more rapidly progressive and can involve the subcutaneous fat, the superficial fascia, and the deep fascia. Early in the process, the overlying skin is often intact, but later, it may become compromised following interruption of the deep blood supply. The condition is clinically distinguished from gas gangrene by the
absence of crepitus and muscle involvement. Early operative exploration is recommended in suspected cases. Group A *Streptococcus* is highly sensitive to penicillin; however, the addition of clindamycin appears to have clinical benefit.\(^8\) Treatment must include early surgical exploration with debridement of involved tissues.

### Seroma and Hematoma

Superficial seroma formation is exceedingly common but rarely has significant clinical consequence. Most seromas can be observed; the rare large seroma that causes troubling symptoms (eg, discomfort) or is cosmetically unacceptable to the patient can usually be managed with a single aspiration or serial aspirations in the office. Refractory large seromas can be treated with percutaneous placement of a drain, which is maintained until the output is low (usually <30 mL/d), or, rarely, excision (ie, capsulectomy).

The more liberal use of aspirin, clopidogrel (Plavix), and heparins in the perioperative period have likely resulted in an increase in the incidence of wound hematoma following abdominal surgery, now in the range of 4% to 8%.\(^8\)\(^2\)\(^3\) Small wound hematomas are of little consequence and usually resolve without intervention. If larger, hematomas may lead to compromise of the overlying skin or predispose to infection. Such hematomas can be aspirated with a large-bore needle or evacuated by opening the wound. If the overlying skin is under tension or ongoing extravasation of blood is noted, hematomas are often better managed in the operating room where active bleeding, if encountered, can be controlled. Reclosure over a drain may limit subsequent seroma accumulation and preserve the integrity of the skin.

### Stitch Abscess

Stitch abscesses or suture sinuses are most often seen at approximately the tenth postoperative day, but may occur earlier or weeks after operation. Stitch abscesses may be superficial or deep. When superficial, they typically present as brown or mauve-colored circumscribed blisters in the line of the incision. The associated pain can be resolved by incising the overlying skin, evacuating the contents, and, if possible, excising residual suture material. Antibiotic treatment is rarely necessary. Deeper stitch abscesses typically
present with an indurated mass. As noted earlier, the use of nonabsorbable suture, such as polypropylene, has been associated with an increased incidence of deep stitch abscesses when compared to closure with a slowly absorbing suture such as polydioxanone.\textsuperscript{35,84} When permanent suture has been used, treatment requires removal of the residual suture material.

**Wound Dehiscence and Evisceration**

Separation of abdominal wounds (ie, dehiscence) with or without protrusion of intra-abdominal contents (ie, evisceration) is a cause of considerable morbidity and mortality. Historically, wound dehiscence rates of up to 10% were reported; contemporary series estimate an incidence between 1% and 3%.\textsuperscript{85,86} Mortality associated with dehiscence has been estimated at 16%.\textsuperscript{84} The mean time to wound dehiscence is 8 to 10 days after operation.\textsuperscript{35,87} Classically, dehiscence is heralded by a sudden rush of pink serosanguinous discharge from the wound. Sometimes, acute presentation with a large subcutaneous hematoma or tympanitic swelling that distends the wound reflecting herniation of bowel through the abdominal fascia is also noted.

As noted earlier, the literature on abdominal closure appears to favor a running mass closure with slowly resorbable or nonresorbable sutures. Notwithstanding such technical considerations, a variety of patient-associated risk factors for dehiscence are recognized and include advanced age (>65 years), hypoalbuminemia, wound infection, ascites, obesity, steroid use, chronic obstructive pulmonary disease, pneumonia, cerebrovascular accident with residual deficit, anemia (ie, hematocrit <30), prolonged ileus, coughing, emergency operation, and operative time greater than 2.5 hours.\textsuperscript{47,86,88} Although some surgeons advocate prophylactic placement of retention sutures in those at high risk for dehiscence, as discussed earlier, there are few data to support this practice.

The cornerstone of treatment of a disrupted wound is immediate reclosure; this is particularly true when dehiscence occurs early in the postoperative period. If evisceration is present, the wound and protruding viscera should be bathed with warm normal saline solution and covered with large sterile dressing prior to prompt transport to the operating room. In the operating room, the prolapsed bowel is restored to the abdominal cavity. Residual suture material is extracted, and necrotic wound edges are debrided.
Reclosure of the fascia is then performed, typically using a monofilament nonabsorbable suture such as polypropylene. Although some surgeons advocate interrupted closure of the fascia following dehiscence, retrospective analyses have failed to demonstrate a reduction in the incidence of late ventral hernia formation with this technique compared to a running closure. The advantage of retention suture placement in this setting is similarly unproven. Retrospective analyses fail to demonstrate any benefit, although a reduction in recurrent evisceration is frequently invoked. Retention sutures are associated with increased discomfort for the patient. Placement of resorbable mesh as an underlay may serve to reinforce the abdominal closure.

On occasion, if the dehiscence is small, the patient is critically ill, or there is no evisceration, nonoperative management is appropriate. In such cases, the wound is packed with a moist sterile dressing. An abdominal binder can be used for further support. The dressing should be changed at regular intervals until the wound fills in with granulation tissue. In some cases, delayed reclosure of the skin can be carried out at this stage. Alternatively, the use of a VAC dressing has been described in this setting.

Incisional Hernia

Incisional hernia formation is the most common long-term complication of abdominal surgery. Documented rates of incisional hernia formation vary widely in the literature. After midline laparotomy, more than 10% of patients develop a hernia. Major risk factors include obesity, diabetes, emergency surgery, postoperative wound dehiscence, smoking, and postoperative wound infection. Repair is discussed extensively elsewhere in this text.

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A hernia is defined as an area of weakness or complete disruption of the fibromuscular tissues of the body wall. Structures within the cavity contained by the body wall can pass through, or herniate through, such a defect. While the definition is straightforward, the terminology is often misrepresented or misused. It should be clear that hernia refers to the actual anatomic weakness or defect, and hernia contents describes those structures that pass through the defect.

Inguinal hernias are among the oldest known afflictions of humankind, and surgical repair of the inguinal hernia is the most common general surgery procedure performed today.¹ Despite the high incidence, the technical aspects of inguinal hernia repair continue to evolve with new surgical advancements.

INGUINAL HERNIA

History

The word “hernia” is derived from a Latin term meaning “a rupture.” The earliest reports of abdominal wall hernias date back to 1500 BC. During this early era, abdominal wall hernias were treated with trusses or bandage.
dressings. The first evidence of operative repair of a groin hernia dates to the first century AD. The original hernia repairs involved wide operative exposures through scrotal incisions requiring orchiectomy on the involved side. Centuries later, around 700 AD, principles of operative hernia repair evolved to emphasize mass ligation and en bloc excision of the hernia sac, cord, and testis distal to the external ring. The first report of groin hernia classification based on the anatomy of the defect (ie, inguinal versus femoral) dates to the 14th century, and the anatomical descriptions of direct and indirect types of inguinal hernia were first reported in 1559.

Bassini revolutionized the surgical repair of the groin hernia with his novel anatomical dissection and low recurrence rates. He first performed his operation in 1884, and published his initial outcomes in 1889. Bassini reported 100% follow-up of patients over a 5-year period, with only five recurrences in over 250 patients. This rate of recurrence was unheard of at the time and marked a distinct turning point in the evolution of herniorraphy. Bassini’s repair emphasizes both high ligation of the hernia sac in the internal ring as well as suture reinforcement of the posterior inguinal canal. The operation also utilizes a deep and superficial closure of the inguinal canal. In the deep portion of the repair, interrupted sutures affixing the transversalis fascia medially to the inguinal ligament laterally repair the canal. This requires an incision through the transversalis fascia. The external oblique fascia provides the superficial closure.

In addition to Bassini’s contributions, Lotheissen in 1898 introduced the first true Cooper’s ligament repair, which affixes the pectineal ligament to Poupart’s ligament and thereby repairs both inguinal and femoral hernia defects. McVay further popularized the Cooper’s ligament repair with the addition of a relaxing incision to reduce increased wound tension.

The advances in groin hernia repair in the century following Bassini have shared the primary goal of reducing long-term hernia recurrence rates. To this end, efforts have been directed toward developing a repair that imparts the least tension on the tissues that are brought together to repair the hernia defect. Darn repairs were first introduced in the early 20th century to reduce wound tension by using either autologous tissue or synthetic suture to bridge the gap between fascial tissues. Muscle and fascial flaps were also attempted without consistent success. In 1918, Handley introduced the first use of silk as a prosthetic darn, with nylon following several years later. However, it was found that heavy prosthetic material increased the risk of wound infection,
and silk suture ultimately lost its strength over time. The use of autologous or synthetic patches was also attempted in order to reduce wound tension and improve rates of recurrence. The first patches, beginning in the early 20th century, consisted of silver wire filigree sheets that were placed along the inguinal canal. Over time, the sheets suffered from metal fatigue, leading to hernia recurrence. Reports of the wire patches eroding into adjacent inguinal structures and even the peritoneal cavity caused yet more concern with this technique. In 1958, Usher introduced the modern synthetic patch, made of a plastic monofilament polymer (polyethylene). Lichtenstein further popularized this technique after developing a sutureless hernia repair using a plastic mesh placed across the inguinal floor.

In the search for a technical means to reduce recurrence, emphasis was also placed on a meticulous dissection that would avoid placement of a prosthetic mesh. The most popular version was the Shouldice technique, initially introduced in 1958, which was in essence a modification of the Bassini operation. This technique involves precise dissection of the entire inguinal floor and closure of the inguinal canal in four layers. The transversalis fascial layer itself is closed in two running layers, as opposed to the single layer of interrupted suture advocated by Bassini. While the operation can be technically challenging to the beginner, it has been associated with excellent long-term outcomes and the lowest reported recurrence rates for non-mesh repairs.

Today, laparoscopic and robotic techniques have been validated as safe and effective in the treatment of groin hernias and as a result, have become commonplace. The laparoscopic approaches were initially developed in the early 1990s when laparoscopic techniques diffused throughout other specialties of general surgery. Robotic inguinal hernia repair has become an area of significant growth in the recent past and continues to grow in volume yearly.

Epidemiology

Seventy-five percent of all abdominal wall hernias are found in the groin, making it the most common location for an abdominal wall hernia. Of all groin hernias, 95% are hernias of the inguinal canal, with the remainder being femoral hernia defects. Inguinal hernias are nine times more common in men than in women. Although femoral hernias are found more often in women,
the inguinal hernia is still the most common hernia in women. The overall lifetime risk of developing a groin hernia is approximately 27% in males and 3% in females. There is also clearly an association between age and hernia diagnosis. After an initial peak in the infant, the prevalence of groin hernias increases with advancing age. On average, the prevalence of hernias is 1.3% for all ages, but increases to 3% in those over the age of 45. In the same way, the complications of hernias (incarceration, strangulation, and bowel obstruction) are found more commonly at the extremes of age. Interestingly, the incidence of inguinal hernia repair actually decreases over the age of 80 for both men and women. It is hypothesized that this is likely due to the increase in comorbidities that supersede the need for hernia repair.

Currently in this country, approximately 800,000 operations for inguinal hernia repair are performed annually. Overall, the lifelong cumulative incidence of an initial unilateral or bilateral inguinal hernia repair in adults is 42.5% for men and 5.8% for women. Nevertheless, in the retrospective review by Zendejas, it was seen that the incidence of inguinal hernia repair is downtrending over time. The etiology of this pattern requires more investigation, but is theorized to be due to a multitude of factors such as the popularization of watchful waiting, as described later, and the increased use of mesh repair which decreases recurrences and need for reoperation.

**Anatomic Classification**

A thorough classification system has been developed to assist in the proper diagnosis and management of the inguinal hernia. All hernias can be broadly classified as congenital or acquired. It is thought that the vast majority of inguinal hernias are congenital in nature. Acquired groin hernias develop after surgical incision and manipulation of the involved abdominal wall tissues. Given the paucity of primary groin incisions utilized in modern general surgery, acquired hernias of the inguinal or femoral region are rare.

Inguinal hernias are further divided by anatomical location into direct and indirect types. This differentiation is based on the location of the actual hernia defect in relation to the inferior epigastric vessels. The inferior epigastric vessels are continuous with the superior epigastric vessels that originate from the internal mammary artery cephalad and ultimately course caudally to become the common femoral artery and vein. These vascular
structures make up the lateral axis of Hesselbach’s triangle, which includes the lateral border of the rectus sheath as its medial border and the inguinal (Poupart’s) ligament itself as the inferior border. Hernias that develop lateral to the inferior epigastric vessels are termed indirect inguinal hernias, and those that develop medial to the vessels are direct inguinal hernias. In this way, direct hernia defects are found within Hesselbach’s triangle. Hernias of the femoral type are located caudal or inferior to the inguinal ligament and medial to the femoral vessels.

The indirect inguinal hernia develops at the site of the internal ring, or the location where the spermatic cord in men and the round ligament in women enters the abdomen. While these may present at any age, indirect inguinal hernias are thought to be congenital in etiology. The accepted hypothesis is that these hernias arise from the incomplete or defective obliteration of the processus vaginalis during the fetal period. The processus is the peritoneal layer that covers the testicle or ovary as it passes through the inguinal canal and into the scrotum in men or the broad ligament in women. During development, the internal ring closes, and the processus vaginalis becomes obliterated following the migration of the testicle into the inguinal canal. The failure of this closure provides an environment for the indirect inguinal hernia to develop. In this way, the remnant layer of peritoneum forms a sac at the internal ring through which intra-abdominal contents may herniate, thereby resulting in a clinically detectable inguinal hernia. Anatomically, the internal ring is lateral to the external ring and the remainder of the inguinal canal, thus explaining the lateral relationship of the indirect inguinal hernia to the inferior epigastric vessels. It is noteworthy that indirect inguinal hernias develop more frequently on the right, where descent of the gonads occurs later during fetal development.

Direct inguinal hernias, in contrast, are found medial to the inferior epigastric artery and vein, and within Hesselbach’s triangle. These hernias are acquired and only rarely found in the youngest age groups. They are thought to develop from an acquired weakness in the fibromuscular structures of the inguinal floor, so that the abdominal wall in this region can no longer adequately contain the intra-abdominal contents. The exact relationship between direct inguinal hernias and heavy lifting or straining remains unclear, and some studies suggest that the incidence of direct hernias is no greater in people in professions that routinely involve heavy manual labor.

While femoral hernias account for less than 10% of all groin hernias, their
presentation can be more acute in nature. In fact, it is estimated that up to 40% of femoral hernias present as emergencies with hernia incarceration or strangulation.\textsuperscript{3} In this way, femoral hernias may also present as bowel obstructions. The empty space through which a femoral hernia forms is medial to the femoral vessels and nerve in the femoral canal and adjacent to the major femoral lymphatics. The inguinal ligament forms the cephalad border of the empty space. However, while the empty space is inferior to the inguinal ligament, the herniated contents may present superior to the ligament, thereby making an accurate diagnosis difficult.

Femoral hernias are much more common in females than males, although inguinal hernias are still the most common hernia in women. The predilection for femoral hernias in women may be secondary to less bulky groin musculature or weaknesses in the pelvic floor tissues from previous childbirth. It has also been shown that previous inguinal hernia repair may be a risk factor for the subsequent development of a femoral hernia.\textsuperscript{3}

Despite the pervasiveness of groin hernias and repairs, there lacks standardization regarding classification of groin hernias. There exist many various classification and grading systems describing inguinal hernias. Early classifications were first seen in the 1960s, and then modified by various groups, including Rutkow and Robbins, Lichtenstein, Nyhus, Zollinger, and Stoppa. Given the variations between individual classifications, the European Hernia Society (EHS) published a simplified yet comprehensive classification based on the Aachen classification.\textsuperscript{8} The EHS grading system describes three characteristics of hernias: whether the hernia is primary or recurrent; the size from 0 to 3, with 0 as no hernia, 1 as <1.5 cm (one finger-width), 2 as <3 cm (two finger-widths), 3 as >3 cm (more than two finger-widths), and × as not investigated; and anatomic location, with L being lateral or indirect, M being medial or direct, and F being femoral. While no consensus exists among surgeons regarding a preferred classification system, it is recommended that the EHS classification be used as a standard to allow for better comparison of hernias and their treatments among various institutions.\textsuperscript{9}

**Anatomy of the Groin**

The boundaries of the inguinal canal must be understood to comprehend the principles of hernia repair. In the inguinal canal, the anterior boundary is the
external oblique aponeurosis; the posterior boundary is composed of the transversalis fascia with some contribution from the aponeurosis of the transversus abdominis muscle; the inguinal and lacunar ligaments impart the inferior border; and the superior boundary is formed by the arching fibers of the internal oblique musculature.

The internal (or deep) inguinal ring is formed by a normal defect in the transversalis fascia through which the spermatic cord in men and the round ligament in women passes into the abdomen from the extraperitoneal plane. The external (or superficial) ring is inferior and medial to the internal ring and represents an opening of the aponeurosis of the external oblique. The spermatic cord passes from the peritoneum through the internal ring and then caudally into the external ring before entering the scrotum in males.

From superficial to deep, the surgeon first encounters Scarpa’s fascia after incising the skin and subcutaneous tissue. Deep to Scarpa’s layer is the external oblique aponeurosis, which must be incised and spread to identify the cord structures. The inguinal ligament represents the inferior extension of the external oblique aponeurosis, and extends from the anterior superior iliac spine to the pubic tubercle. The medial extension of the external oblique aponeurosis forms the anterior rectus sheath. The iliohypogastric and ilioinguinal nerves, which provide sensation to the skin, penis, and the upper medial thigh, lie deep to the external oblique aponeurosis in the groin region. The internal oblique aponeurosis is more prominent cephalad in the inguinal canal, and its fibers form the superior border of the canal itself. The cremaster muscle, which envelops the cord structures, originates from the internal oblique musculature. The transversus abdominis muscle and its fascia represent the true floor of the inguinal canal. Deep to the floor is the preperitoneal space, which houses the inferior epigastric artery and vein, the genitofemoral and lateral femoral cutaneous nerves, and the vas deferens, which traverses this space to join the remaining cord structures at the internal inguinal ring.

**Etiology**

The indirect inguinal hernia, the most common form of groin hernia across all ages and genders, is thought to be congenital in etiology. The processus vaginalis is the pocket of peritoneum that forms around the testicle as it descends through the internal ring and along the inguinal canal into the
The scrotum during the 28th week of gestation. The primary etiology behind the indirect inguinal hernia is believed to be a patent processus vaginalis, which in essence represents a hernia sac. In this way, the hernia defect is the internal ring itself, and the sac is preformed but never closed at the end of gestation. Once intra-abdominal contents find their way into the sac, an indirect inguinal hernia is formed.

However, not every person with a patent processus vaginalis develops an inguinal hernia during his or her lifetime. Thus, other predisposing factors must aid in indirect inguinal hernia formation. It is commonly thought that repeated increases in intra-abdominal pressure contribute to hernia formation; hence, inguinal hernias are commonly associated with pregnancy, chronic obstructive pulmonary disease, abdominal ascites, patients who undergo peritoneal dialysis, laborers who repeatedly flex abdominal wall musculature, and individuals who strain from constipation. It is also thought that collagen formation and structure deteriorates with age, thus explaining increased hernia formation in older individuals.

Several inborn errors of metabolism can lead to hernia formation. Specifically, conditions such as Ehlers–Danlos syndrome, Marfan syndrome, Hunter syndrome, and Hurler syndrome can predispose to defects in collagen formation, resulting in weaknesses in the abdominal wall. There is also evidence that cigarette smoking is associated with connective tissue disruption, and not surprisingly, hernia formation is more commonly found in the chronic smoker.

**Clinical Manifestations**

The groin hernia can present in a variety of ways, from the asymptomatic hernia to frank peritonitis in a strangulated hernia. Many hernias are found on routine physical examination or on focused examination for an unrelated complaint. These groin hernias are usually fully reducible and chronic in nature. Such hernias are still referred for repair since they invariably develop symptoms, and asymptomatic hernias still have an inherent risk of incarceration and strangulation, albeit low.\(^{10,11}\)

The most common presenting symptomatology for a groin hernia is a bulge associated with a dull feeling of discomfort or heaviness in the groin region that is exacerbated by straining the abdominal musculature, lifting
heavy objects, or defecating. These maneuvers worsen the feeling of discomfort by increasing the intra-abdominal pressure and forcing the hernia contents through the hernia defect. Pain develops as a tight ring of fascia outlining the hernia defect compresses intra-abdominal structures with a visceral neuronal supply. With a reducible hernia, the feeling of discomfort resolves as the pressure is released when the patient stops straining the abdominal muscles. The pain is often worse at the end of the day, and patients in physically active professions may experience the pain more often than those who lead a sedentary lifestyle.

Overwhelming or focal pain from a groin hernia is unusual and should raise the suspicion for hernia incarceration or strangulation. An incarcerated hernia occurs when the hernia contents are trapped in the hernia defect so that the contents cannot be reduced back into the abdominal cavity. The tight circumferential pressure applied by the hernia defect serves to impede the venous outflow from the hernia contents, resulting in congestion, edema, and tissue ischemia. Ultimately, the arterial inflow to the hernia contents is compromised as well, resulting in tissue loss and necrosis, termed strangulation of the hernia.

All types of groin hernias are at risk for incarceration and strangulation, although the femoral hernia seems to be predisposed to this complication. Incarceration and strangulation of a groin hernia may present as a bowel obstruction when the tight hernia defect constricts the lumen of the viscus. Hence, all patients presenting with bowel obstruction require a thorough physical examination of the groin region for inguinal and femoral hernias.

The physical exam differs between an incarcerated and a strangulated hernia. The incarcerated hernia may be mildly tender due to venous congestion from the tight defect. If there is no bowel in the hernia sac, an incarcerated groin hernia may alternatively present as a hard, painful mass that is tender to palpation. The strangulated hernia will be tender and warm and may have surrounding skin erythema secondary to the inflammatory reaction from the ischemic bowel. The patient with the strangulated hernia may have a fever, hypotension from early bacteremia, and a leukocytosis. The incarcerated hernia requires operation on an urgent basis within 6 to 12 hours of presentation. If the operation is delayed for any reason, serial physical exams are mandated to follow any change in the hernia site indicating the onset of tissue loss. The strangulated hernia clearly requires emergent operation immediately following diagnosis.
It may also be difficult to differentiate fat from bowel contents in the hernia sac; incarcerated omental fat alone can produce significant pain and tenderness on physical exam, similar to incarcerated bowel.

**Pregnancy and Groin Hernia**

Not surprisingly, groin hernias during pregnancy may become symptomatic. This is related to the increased intra-abdominal pressure from the growing fetus and enlarging uterus. The symptomatic groin discomfort may become positional later in pregnancy as the uterus shifts location with movement. While the risks of complications of groin hernias still exist during pregnancy, the enlarging uterus may in theory protect against incarceration by physically blocking the intra-abdominal contents from the inlet of the defect.

In general, elective repair of groin hernias during pregnancy is not recommended, even if they become increasingly symptomatic. However, emergent repair of the incarcerated or strangulated hernia is undertaken as needed.

**Physical Examination**

As with any hernia, the groin hernia should be properly examined with the patient in the standing position. This allows the hernia contents to fill the hernia sac and make the hernia more obvious on physical examination. Some hernias, however, may be easily identifiable in the supine position. It should be noted that the exact anatomical classification of the inguinal hernia (ie, indirect versus direct) is difficult to accurately predict based on physical exam alone, and likely not clinically relevant, as all repair techniques should address both direct and indirect inguinal hernias.

In the male patient, using the second or third finger, the examiner should invaginate the scrotum near the external ring and direct the finger medially toward the pubic tubercle. The examiner’s finger will thus lie on the spermatic cord with the tip of the finger within the external ring. The patient is then asked to cough or perform a Valsalva maneuver. A true inguinal hernia will be felt as a silk-like sensation against the gloved finger of the examiner. This is the infamous “silk glove” sign.

The female patient does not have the long and stretched spermatic cord to
follow with the examiner’s finger during the physical examination. Instead, two fingers can be placed along the inguinal canal, and the patient is asked to cough or strain. If present, the examiner should feel the sensation of the hernia sac against the gloved finger. Particular attention in the female patient should be paid to the location of the sensation. Femoral hernia sacs will present medial and just inferior to the lower border of the inguinal ligament, while inguinal hernias will present superior to the lower border of the inguinal ligament.

While the physical examination does not differ in the infant, it can be more challenging to elicit the hernia impulse given the compressed groin anatomy of the young child. It is well known that a groin hernia can be more readily diagnosed in the infant who is actively crying and hence increasing the intra-abdominal pressure through flexion of the abdominal wall musculature.

The examination for the femoral hernia in both genders involves palpation of the femoral canal just below the inguinal ligament in the upper thigh. In this way, the most easily palpable landmark is the femoral artery, which is located lateral in the canal. Medial to the femoral artery is the femoral vein, and the femoral empty space is just medial to the vein. This area can be located easily, palpated with two fingers, and then examined closely while the patient coughs or strains. In general, a focused groin hernia examination should involve the investigation for both inguinal and femoral hernias in both genders.

**Treatment**

The treatment of all hernias, regardless of their location or type, is surgical repair. Elective repair is performed to alleviate symptoms and to prevent the significant complications of hernias, such as incarceration or strangulation. While the limited data available on the natural history of groin hernias show that these complications are rare, the complications are associated with a high rate of morbidity and mortality when they do occur. At the same time, the risks of elective groin hernia repair, even in the patient with a complicated medical history, are exceedingly low. Outcomes of surgical repair are generally excellent with minimal morbidity and relatively rapid return to baseline health.

The major risk with delayed surgical repair is the risk of incarceration
and/or strangulation. It is not possible to reliably identify those hernias that are at an increased risk for these complications. It is known that the risk of incarceration of a hernia is greatest soon after the hernia manifests itself. This is likely due to the fact that at the early stage of the hernia, the defect is small and fits tightly around the hernia sac; therefore, any contents that fill the sac may quickly become trapped within the hernia. Over time, the hernia defect stretches due to the tissue that enters and leaves the sac with changes in intra-abdominal pressure. After 6 months, the risk of hernia incarceration decreases from 5% per year to 1% to 2% per year. In general, the larger the palpable defect on physical examination, the lower the risk of incarceration. Clearly, all risks of tissue loss aside, elective hernia repair is still preferred over emergent repair.

While elective hernia repair is recommended, for those with minimal symptoms who do not wish to undergo surgical intervention, watchful waiting is a reasonable and safe option. In the watchful waiting trial, 720 men with minimally symptomatic or asymptomatic inguinal hernias were enrolled and randomized to either watchful waiting or open surgical repair.\textsuperscript{10} The study showed that watchful waiting is a safe alternative to surgery. After 4 years, only two patients required emergent operation for either acute incarceration without strangulation or bowel obstruction and only a total of three patients required emergency operations at 7 years.\textsuperscript{10,11} This changed the traditional idea that all groin hernias should be repaired immediately. Nevertheless, it should be noted that while watchful waiting is safe with low risk of need for emergent surgery, 68% of patients who waited eventually underwent surgical repair, most commonly due to worsening hernia-related pain. It was also seen that men older than 65 years of age had increased rates of surgical repair than younger men for pain (79% crossover to surgical repair vs 62%). Therefore, while watchful waiting is a safe option, the majority of patients will likely experience progression of symptoms that may require surgical repair. As a result, elective hernia repair still remains the preferred treatment and should be offered to all surgical candidates.

\textbf{Anesthesia}

Groin hernia repair can be performed using a variety of anesthesia options, including general, regional (such as spinal or epidural), and local
anesthesia. Laparoscopic repairs usually require general anesthesia in order to provide the complete muscle relaxation needed to achieve insufflation of the preperitoneal or peritoneal space.

Open groin hernia repairs are frequently performed using either regional or local anesthesia. Local anesthesia with controlled intravenous sedation, referred to as monitored anesthesia care, is often preferred in the repair of the reducible inguinal hernia. Its advantages include the ease of induction and awakening, the short postanesthesia recovery period, and the fact that its intensity can easily be titrated up or down based on patient comfort levels intraoperatively. The only major disadvantage to this approach is in patients who experience considerable pain during repairs of large groin hernias.

In groin hernia repair, local anesthesia can be administered either as a direct infiltration of the tissues to be incised or as a local nerve block of the ilioinguinal and iliohypogastric nerves. The latter is associated with improved local pain control, but may be difficult to achieve. The local nerve block also spares the soft tissue edema from diffuse infiltration of local anesthesia.

Spinal or continuous epidural anesthesia allows the surgeon greater freedom to maneuver within the operative field since the anesthetized region is larger than in local anesthesia. However, these modes of anesthesia carry their own infrequent risks such as urinary retention, prolonged anesthetic effect, hypotension, and spinal headache. They may also be associated with longer in-hospital recovery times on the day of surgery.

A randomized trial of local, regional, and general anesthesia in 616 adult patients undergoing open inguinal hernia repair in 10 hospitals found that local anesthesia was superior in the early postoperative period. Compared to those who received regional or general anesthesia, patients who received local anesthesia had less postoperative pain and nausea, shorter time spent in the hospital, and fewer unplanned overnight admissions (3% vs 14% and 22%, respectively).

**Operative Techniques**

Successful surgical repair of a hernia depends on a tension-free closure of the hernia defect to attain the lowest possible recurrence rate. Previous efforts to simply identify the defect and suture it closed resulted in unacceptably high recurrence rates of up to 15%. Modern techniques have improved upon this
recurrence rate by utilizing the placement of mesh over the hernia defect, or in the case of laparoscopic repair, behind the hernia defect. One exception to this rule is the classic Shouldice repair, which uses meticulous dissection and closure without mesh placement to obtain a consistently low recurrence rate. Another benefit of the tension-free closure is that it has been shown to cause significantly less pain and discomfort in the short-term postoperative period.

Figure 11-1 illustrates the essential steps to the modern open inguinal hernia repair. All of the open anterior herniorrhaphy techniques begin with a transversely-oriented, slightly curvilinear skin incision of approximately 6 to 8 cm, positioned one to two fingerbreadths above the inguinal ligament. Dissection is carried down through the subcutaneous and Scarpa’s layers. The external oblique aponeurosis is identified and cleaned so that the external ring is identified inferomedially. Being careful to avoid injury to the iliohypogastric and ilioinguinal nerves, the aponeurosis is incised sharply and opened along its length through the external ring with fine scissors. The nerves underlying the external oblique fascia are then identified and preserved without mobilization to decrease the risk of post-herniorrhaphy inguinodynia. Additionally, the iliohypogastric nerve and the genital branch of the genitofemoral nerve should be identified and preserved without mobilization in order to retain their protective investing fascial layers. The soft tissue is cleared off the posterior surface of the external oblique aponeurosis on both sides and the spermatic cord is mobilized. Using a combination of blunt and sharp dissection, the cremaster muscle fibers enveloping the cord are separated from the cord structures and the cord itself is isolated. At this point, it is possible to accurately define the anatomy of the hernia. An indirect hernia will present with a sac attached to the cord in an anteromedial position extending superiorly through the internal ring. A direct inguinal hernia will present as a weakness in the floor of the canal posterior to the cord. A pantaloon defect will present as both a direct and indirect defect in the same inguinal canal.
FIGURE 11-1 Adult hernia incision and dissection. **A.** Transverse incision. **B.** Curved skin crease incision. **C.** The aponeurosis of the external oblique is incised along the direction of its fibers. **D.** The inguinal canal is exposed and the spermatic cord mobilized. **E.** The spermatic cord has been skeletonized, and the internal ring and posterior wall of the canal (the transversalis fascia) have been defined. **F.** A medium-sized sac has been dissected free of the cord elements. **G.** The sac has been invaginated. **H.** A long or complete sac is being dissected free close to the internal ring. **I.** The sac has been transected.

The specifics of the common modern techniques for hernia repair will be discussed further.

**THE SHOULDICE TECHNIQUE**

The Shouldice technique is commonly used for open repair of inguinal
hernias and is the most popular pure tissue hernia repair. It is in essence the modern evolution of the Bassini repair performed in a multilayered fashion. Both operations use a tightening of the internal ring and closure of the transversalis fascia to the inguinal ligament as their primary tenets of hernia repair.¹⁴

Figure 11-2 illustrates the basic steps in the Shouldice repair. After suitable exposure and isolation of the cord, a pair of scissors is passed posterior to the transversalis fascia beginning at the medial pillar of the internal ring and extending inferomedially to the pubic tubercle. In this way, the transversalis fascia is separated from the preperitoneal fat plane. Care must be taken at this stage to preserve the inferior epigastric vessels that reside in the preperitoneal space. The transversalis fascia is then opened with scissors along the entire inguinal floor from internal ring to pubic tubercle, and the posterior surface of the transversalis is cleaned of its preperitoneal attachments. As the first layer of the repair, the free edge of the lower transversalis flap is sutured in a continuous, imbricated fashion behind the upper flap to the posterior surface of the upper transversalis fascia and the lateral component of the posterior rectus sheath. This running suture layer is started medially at the pubic tubercle and carried up to and through the internal ring, thereby tightening the transversalis fascia around the cord at its entrance to the inguinal canal. The first layer is not tied but continued in a running fashion from lateral to medial as a second layer closing the upper transversalis flap to the base of the lower edge as well as the inguinal ligament. This second layer progresses medially to the pubic tubercle where it is tied to the original tail that started the first layer. The third layer of continuous suture starts at the tightened internal ring and brings together the conjoined tendon (the internal oblique and transversus abdominis aponeuroses) medially with the inguinal ligament laterally. This layer is run down to the pubic tubercle, and returns back to the internal ring as the fourth layer including the anterior rectus sheath medially with the posterior aspect of the external oblique aponeurosis laterally. The cord can now be relaxed gently on the new inguinal floor, and the external oblique aponeurosis is closed in one to two additional continuous layers extending down to the external ring to reapproximate this structure. The original descriptions of the operation by Shouldice used continuous stainless steel wire suture for all four layers of repair, although surgeons commonly use permanent synthetic suture today.
The Shouldice Hospital reports excellent long-term outcomes from their technique with recurrence rates less than 1% in selected patients.\textsuperscript{15,16} These results have not been achieved with any other pure tissue technique. The operation is well tolerated by most patients using local anesthesia only. From the multiple, overlapping, continuous suture lines, Shouldice proponents argue that any tension brought about in this type of closure is dispersed throughout the entire inguinal canal. The dissection is complicated, however, and requires excellent surgical technique and anatomic awareness. Moreover, other surgeons utilizing the Shouldice method have not achieved recurrence rates this low. Thus, the low rate of recurrence associated with the Shouldice technique likely depends on the level of surgical expertise and the patient selection. In one report of 183 inguinal hernia repairs using the Shouldice technique under local anesthesia, the recurrence rates for beginners versus more experienced surgeons were 9.4% versus 2.5%, respectively.\textsuperscript{17}

A recent meta-analysis conducted by the Cochrane Collaboration compared the Shouldice technique with other open techniques for inguinal hernia repair.\textsuperscript{18} The analysis incorporated results from 16 different randomized or quasi-randomized studies and compared 2566 hernias repaired via the Shouldice technique with 1121 hernias repaired with mesh and 1608 hernias repaired with other non-mesh techniques. The recurrence rate for the Shouldice repair was significantly higher than mesh repair (odds ratio 3.8), but significantly lower than non-mesh repair (odds ratio 0.62). There were no significant differences between the groups with respect to complications, length of stay, or chronic pain following herniorraphy. Thus, the Shouldice technique is less preferable than mesh repairs with respect to recurrence, but appears to be the repair of choice in situations where mesh cannot be implanted.

**THE COOPER’S LIGAMENT REPAIR**
The Cooper’s ligament repair is the only open tissue–based technique that definitively repairs both inguinal and femoral hernia defects in the groin. The operation is often named after Chester McVay, who popularized the operation in the 1940s and introduced the concept of the relaxing incision to decrease the tension from the repair. The repair is also a primary tissue repair in that no mesh is utilized.

The Cooper’s ligament repair begins similar to the Shouldice procedure, and exposure and isolation of the cord is performed. The transversalis fascia is then opened and cleaned posteriorly. At this time, Cooper’s ligament is identified and dissected free of its fibrous and fatty attachments. The defects are repaired by using interrupted suture to affix the upper border of the transversalis fascia to Cooper’s ligament beginning medially at the pubic tubercle and continuing until the femoral sheath is reached. At this point, the femoral canal is closed by carefully suturing Cooper’s ligament to the femoral sheath. The repair is continued by transitioning anteriorly from Cooper’s ligament with interrupted sutures between the transversalis fascia and the iliopubic tract laterally until the entrance point of the cord is reached. In this way, the closure creates a new and tighter internal inguinal ring around the cord.

The Cooper’s ligament repair frequently requires a relaxing incision because this pure tissue repair is associated with significant tension created by closing all three groin hernia defects. After the transversalis fascia has been mobilized, and prior to the closure of the fascia to Cooper’s ligament, a 2- to 4-cm vertical incision is made at the lateral border of the anterior rectus sheath beginning at the pubic tubercle and extending superiorly. The relaxing incision can be left open since the rectus muscle should protect against any herniation; alternatively, some surgeons argue for placement of a mesh over the relaxing incision since hernia formation can occur at this site.

The Cooper’s ligament repair is an outstanding technique for a femoral hernia and is associated with excellent long-term results in experienced hands. Disadvantages of the repair include a longer operating time, a more extensive dissection, the potential for vascular injury and thromboembolic complications from the femoral vessels, and a longer postoperative recovery phase.

Prosthetic Repairs
Polypropylene mesh is the most common prosthetic used today in mesh repairs of the inguinal hernia. The two most common prosthetic repairs are the Lichtenstein\textsuperscript{19} and the “plug and patch” repair as described by Gilbert\textsuperscript{20} and popularized by Rutkow and Robbins.\textsuperscript{21}

The type of mesh to be used during prosthetic inguinal hernia repairs deserves a brief discussion. The most common and preferred mesh for groin hernia repair is a polypropylene woven mesh marketed under a variety of names. Polypropylene is preferred because it allows for a fibrotic reaction to occur between the inguinal floor and the posterior surface of the mesh, thereby forming scar and strengthening the closure of the hernia defect. This fibrotic reaction is not seen to the same extent with other varieties of prosthetic, namely, expanded polytetrafluoroethylene (PTFE) mesh. PTFE is sometimes used for repair of ventral or incision hernias in which the fibrotic reaction with the underlying serosal surface of the bowel is best avoided. In addition, multiple studies demonstrate that lightweight versions of polypropylene have been associated with a decreased risk of chronic groin pain following inguinal hernia repair and are preferred to heavier weight versions of the same mesh.\textsuperscript{22–25}

There are limited prospective, randomized data comparing the recurrence rate of open repairs with and without mesh. An attempted meta-analysis concluded that mesh repair was associated with fewer overall recurrences, although the authors report that formal analysis was limited by the lack of available study data.\textsuperscript{26} In the review by Cochrane Collaboration and EU Hernia Trialists Collaboration, it was shown that there were lower rates of recurrence following mesh repair than non-mesh repair.\textsuperscript{25} A review of 26,000 inguinal hernia repairs from Denmark further found that mesh repairs had a lower reoperation rate than conventional open repairs.\textsuperscript{27} Therefore, the EHS recommends open mesh repair over open non-mesh repair; if non-mesh repair is considered, the Shouldice technique is the recommended procedure.\textsuperscript{9} More than 90\% of groin hernia repairs performed in the United States in the modern era utilize mesh placement.\textsuperscript{6}

**THE LICHTENSTEIN TECHNIQUE**

The Lichtenstein inguinal hernia repair was the first pure prosthetic, tension-free repair to achieve consistently low recurrence rates in long-term outcomes.
analysis. This operation begins with the incision of the external oblique aponeurosis and the isolation of the cord structures. Any indirect hernia sac is mobilized off the cord to the level of the internal ring. At this point, a large mesh tailored to fit along the inguinal canal floor is placed so that the curved end lies directly on top of the pubic tubercle. The mesh patch extends underneath the cord until the spermatic cord and the tails of the mesh patch meet laterally. Here, an incision is made in the mesh, and the cord is inserted between the tails of the mesh, thereby creating a new, tighter, and more medial internal ring. The tails are sutured together with one nonabsorbable stitch just proximal to the attachment of the cord. The mesh is then sutured in a continuous or interrupted fashion to the pubic tubercle inferiorly, the conjoined tendon medially, and the inguinal ligament laterally. Care must be taken not to incorporate the iliohypogastric nerve during fixation of the cephalad portion of the mesh, and thus identification of this nerve prior to mesh fixation is strongly advised.

Rutkow and Robbins have reported interesting and effective advances in the Lichtenstein technique. The “plug and patch” repair, as illustrated in Figure 11-3, represents a tension-free herniorraphy and can even be performed without sutures. In this technique, the patch is placed in a similar fashion to the modern Lichtenstein repair as it lies along the inguinal canal from the pubic tubercle medially to beyond the cord laterally. In addition, a mesh plug in the form of an umbrella or cone is snugly fit up and into the internal ring. In this way, the repair goes beyond just a tightening of the internal ring, but serves to close the ring around the spermatic cord. Modifications of this operation exist and are practiced commonly by general surgeons. The patch and plug can be sutured to the surrounding inguinal canal tissue in an interrupted or continuous fashion. Alternatively, both prostheses can be placed in appropriate position with no suture affixment. In this way, the body’s natural scarring mechanism will hold both pieces of mesh in place over time. Wide internal ring defects, often caused by large or chronic indirect sacs, may require one or two sutures to tack the plug in place to avoid slippage into the canal anteriorly or the retroperitoneal space posteriorly. While this technique is employed by many surgeons, mesh plugs may be associated with an increased rate of nociceptive chronic groin pain and should likely be avoided in thin patients who are more likely to sense a meshoma.
FIGURE 11-3  The sutureless “patch and plug” tension-free inguinal hernia repair.  A.  The polypropylene mesh “umbrella plug” being passed through the internal ring.  B.  The “umbrella plug” has opened behind the transversalis fascia.  C.  The polypropylene mesh laid down onto the posterior wall of the inguinal canal (the transversalis fascia).  Note the end tails of the mesh patch.
embracing the cord.

**THE PREPERITONEAL APPROACH**

The preperitoneal space is found between the transversalis fascia and the peritoneum itself. The actual groin hernia defect is located anterior to this space, whether the defect exists in the internal ring (indirect inguinal hernia) or through the transversalis floor of the inguinal canal (direct inguinal hernia). Several authors, including Rives, Nyhus, Stoppa, and Kugel, advocate the use of a preperitoneal or posterior approach to repair of the inguinal hernia. They argue that this approach is more effective than the traditional anterior herniorrhaphy because a repair in the preperitoneal plane fixes the hernia defect in the space between the hernia contents and the hernia defect. In contrast, the anterior approach does not keep the hernia contents from contact with the defect, but rather fixes the hernia defect anterior to the defective anatomy. The operation is also advocated for difficult inguinal hernia recurrences, since the posterior approach will usually remain open and without scar following a previous anterior hernia repair. The original operation as described by Nyhus repairs the hernia primarily with suture, although more recent modifications incorporate a mesh patch posterior to the floor of the inguinal canal. As described later in this chapter, the standard laparoscopic technique for inguinal hernia repair is based entirely on the preperitoneal hernia repair.

Figures 11-4 and 11-5 illustrate the preperitoneal repair as described by Rives. In the preperitoneal hernia repair, the incision is usually made transversely in the lower quadrant 2 to 3 cm cephalad to the inguinal ligament. The incision is made slightly more medial than the anterior approach so that the lateral border of the rectus muscle can be exposed after incising the anterior rectus sheath. Once the muscle is exposed, retraction of the rectus muscle medially allows for careful opening of the posterior rectus sheath and entry into the preperitoneal space. The inferior epigastric vessels and the cord can be visualized in this space. The cord usually does not require extensive manipulation or dissection since the usual cord attachments (lipoma and cremaster fibers) are found in the anterior layers of the inguinal canal. In this way, the approach also avoids exposure to the sensory nerves of the inguinal canal.
**FIGURE 11-4** Rives prosthetic mesh repair. **A.** Lower line of fixation of the mesh. **B.** Lateral and upper points of fixation of the mesh. **C.** Preperitoneal placement of the mesh and the Bassini-type repair of the posterior wall of the inguinal canal anterior to the mesh.

**FIGURE 11-5** **A.** The lower midline incision used for the preperitoneal approach to inguinal hernia repair. **B.** Another view of the points of attachment of the mesh in the preperitoneal plane.
Once the preperitoneal space has been entered and exposed, the specific repair to be performed depends on hernia anatomy. For direct defects, the sac is inverted back into the peritoneal cavity but does not need to be excised. The transversalis fascia is then reapproximated over the inverted sac using interrupted sutures; in this way, the upper border of the transversalis fascia is affixed to the lower border composed of the iliopubic tract. For indirect defects, the sac is reduced off of the cord and a high ligation of the sac is performed at the sac neck; ironically, with this approach, the “high ligation” is actually a “posterior” ligation, since the surgeon ideally should transect the sac just above the preperitoneal fat, which is situated along the inferior border of the exposed field. Once the sac has been ligated, the defect in the internal ring is repaired from the posterior plane using interrupted suture to affix the ring leaflets of the transversalis fascia to the iliopubic tract thereby tightening the ring itself.

Modifications of this approach using the prosthetic mesh patch are relatively straightforward. The mesh patch is placed underneath the transversalis fascia and directly on the preperitoneal fat. This patch, if placed completely over the inguinal region, covers any peritoneum that could potentially form a hernia sac through the myopectineal orifice.

THE ONSTEP TECHNIQUE

The Onstep technique is a novel method of hernia repair initially described by Lourenco and da Costa in 2013. It is in essence a modified preperitoneal approach that also utilizes a prosthetic mesh for a tension-free repair.\textsuperscript{29} Similar to a preperitoneal repair, the Onstep procedure involves an incision two finger-widths lateral to the midline and two finger-widths superior to the pubic symphysis, more cranial than the incision seen with the Lichtenstein repair. Dissection is then taken down through subcutaneous tissue, Scarpa’s fascia, and the anterior surface of external oblique aponeurosis to expose the internal oblique aponeurosis. The space between the internal and external obliques is then bluntly dissected and the cord elevated out of the incision. If an indirect hernia is encountered, the hernia contents are reduced and the sac ligated or excised. If a direct hernia is encountered, the hernia sac is dissected from surrounding tissues and both the hernia sac and contents are reduced back into the abdominal cavity. After management of the hernia sac and contents, the transversalis fascia is bluntly perforated over the pubis and the
dissection bluntly continued to the posterior surface of the pubic bone in order to find the preperitoneal space. The mesh used in the original description of the Onstep procedure is the PolySoft™ hernia patch. The medial aspect of the mesh is placed in the preperitoneal space, while the lateral tails of the mesh, created by cutting an axial slit into the mesh, enclose the spermatic cord and lie in the plane between the internal and external obliques.  

In the original study published by Lourenco and da Costa, 693 patients underwent the Onstep procedure, with an overall complication rate of 1.0% at 1 year. Five patients experienced early complications of seroma, hematoma, and wound infection. Four patients had residual pain at 6 months; three of these patients required reoperation and removal of the recoil ring in the mesh under local anesthesia, with resolution of the pain by 12 months. The recurrence rate was found to be 0.6%; all recurrences occurred in the first 2 months after surgery. The Onstep procedure was further studied in 80 patients at Herlev Hospital in Copenhagen, which showed that with 85% follow-up, 95.5% reported no pain after an Onstep repair.  

**Laparoscopic Repair**

Laparoscopic groin hernia repair was first performed by Ger in 1979, although it is only within the past decade and a half that laparoscopic hernia repair has become more accepted. The laparoscopic approach to hernia repair has since evolved into a common and effective procedure. Today, the laparoscopic approach comprises approximately 20% to 25% of groin hernia operations, and 80,000 to 100,000 laparoscopic hernia repairs are performed annually in the United States. The most important difference between the laparoscopic and open approaches for inguinal hernia repair is anatomical: the laparoscopic approach uses mesh to repair the hernia defect in a plane posterior to the defect (either in the preperitoneal space or from within the peritoneal cavity), whereas the open approaches repair the hernia anterior to the defect.

Three different techniques exist for laparoscopic repair of groin hernias. The transabdominal preperitoneal (TAPP) repair involves standard laparoscopy with access into the peritoneal cavity and placement of a large mesh along the anterior abdominal wall, thereby repairing the hernia
posterior to the defect. This technique was the first laparoscopic hernia repair to be performed. Ports are generally placed through the umbilicus and then laterally at the midclavicular line at the level of the umbilicus. The hernia defect is usually well visualized from within the peritoneal cavity. After both inguinal regions have been inspected and laparoscopic adhesiolysis performed if necessary, the median umbilical ligament (the urachal remnant), the medial umbilical ligament (the remnant of the umbilical artery), and the lateral umbilical fold (the reflection of peritoneum over the inferior epigastric vessels) are identified. The parietal layer of peritoneum is then incised from the medial umbilical ligament out laterally toward the anterior superior iliac spine superior to the hernia defect and reflected inferiorly, thereby exposing the hernia defect, the epigastric vessels, Cooper’s ligament, the pubic tubercle, and the iliopubic tract. The cord structures are then dissected free of their peritoneal attachments. The bladder is subsequently mobilized in the space of Retzius in order to visualize Cooper’s ligaments on both sides. In a direct hernia, the peritoneal sac is pulled back within the peritoneal cavity with gentle traction to separate the thin peritoneal layer from the equally thin layer of transversalis fascia anterior to it. In an indirect hernia, the peritoneal sac is retracted off of the cord structures and pulled back within the peritoneal cavity. Alternatively, in the setting of a large chronic indirect hernia, the sac can be divided distally to the internal ring so that only the proximal portion of the sac needs to be mobilized for the repair. A large polypropylene or polyester mesh patch is then placed between the peritoneum and the transversalis fascia that covers the entire myopectineal orifice. The mesh is stapled or tacked to the pubic tubercle medially, Cooper’s ligament inferiorly, and the anterior superior iliac spine laterally. Alternatively, anatomic or self-gripping meshes can be utilized without any additional fixation. The incised peritoneal flap is then closed over the mesh via suturing or tacking.

With increasing popularity of robotic-assisted surgery, it is not surprising that this technology has spread to the surgical repair of hernias, with the development of robotic-assisted TAPP. Robotic TAPP was first performed concomitantly during robotic-assisted radical prostatectomies. These initial studies showed great success, demonstrating no complications of mesh placement, wound infection, chronic pain, and fluid collections, and a 2.6% recurrence rate. This led to further experiences with robotic TAPP, which has been described to have better visualization of surgical field and improved maneuverability compared with traditional laparoscopy. Port placement,
dissections, and repair of the hernia are similar to that of laparoscopic TAPP as described previously. In the results published by Escobar Dominguez and associates, 123 hernias in 78 patients were repaired with robotic TAPP using the da Vinci platform.\textsuperscript{33} Forty-five of these procedures were bilateral robotic herniorrhaphies. Results showed no mortalities or conversions to open procedures. The complication rate was 11.5%, similar to the published TAPP and total extraperitoneal (TEP) complication rates of 8% to 28% and 4% to 24%, respectively, leading to the conclusion that robotic TAPP is a safe and effective method of hernia repair.

Recently, with improvement in robotic technologies, there has also been the development of robotic-assisted single-site hernia repair, which utilizes a single umbilical port, as opposed to the traditional three ports described in robotic TAPP. In a case study by Bosi and associates, they describe use of robotic-assisted single-site hernia repair for bilateral inguinal hernia repair that demonstrated no postoperative complications.\textsuperscript{34} However, it should be noted that robotic TAPP is limited by high operating costs and need for robotic training by the surgical team.

The intraperitoneal onlay mesh technique (IPOM) was developed as a simplified version of the TAPP repair. In this technique, laparoscopic exposure is obtained directly into the peritoneal cavity as in the TAPP. However, this technique does not require an extensive mobilization of the peritoneal flap and dissection of the preperitoneal space. Rather, a large mesh is simply stapled or sutured directly posterior to the peritoneum to repair the hernia. In theory, once the peritoneum scars to the mesh after allowing for connective tissue ingrowth, the peritoneum will not be mobile enough to herniate through the actual defect and intra-abdominal pressure will keep the abdominal contents posterior to the mesh patch. The disadvantage of this procedure is that there is direct exposure of mesh to the intra-abdominal contents and therefore a high risk of adhesion formation and possible erosion of the mesh into bowel contents. Another potential disadvantage of the IPOM is that in large inguinal hernias, the mesh and peritoneum may herniate through the defect together, thereby negating any protective effect imparted by the mesh patch. Therefore, at the present time, this procedure is thought to be experimental only.

While the TAPP repair has been shown to be effective, there is a risk that the prosthetic mesh will be in direct contact with the bowel, and significant concern has been raised about the potential for intra-abdominal adhesions
Although enthusiasm for this technique has waned in recent years with the advent of TEP laparoscopic approaches to inguinal hernia repair, studies have shown no difference in short- or long-term outcomes between TAPP and TEP.

The TEP approach to laparoscopic inguinal hernia repair is currently the most popular laparoscopic technique. This repair is performed entirely within the preperitoneal space and does not involve the peritoneal cavity when performed correctly. In this technique, the surgeon carefully develops a plane between the peritoneum posteriorly and the abdominal wall tissues anteriorly, thus insufflating the preperitoneal space. An incision is made inferior to the umbilicus, and the anterior rectus sheath on the ipsilateral side is incised. The rectus muscle is retracted laterally, and the preperitoneal space is bluntly dissected to allow placement of a balloon port to facilitate insufflation. Once the space has been insufflated, two additional ports are placed in the midline between the umbilicus and the pubic symphysis. In experienced hands, this approach provides for excellent visualization of the groin anatomy, and the dissection proceeds in a similar fashion to the TAPP. The TEP repair allows a large prosthetic mesh to be placed through a laparoscopic port into the preperitoneal space, and it is then positioned deep to the hernia defect to repair the hernia from a posterior approach.

There are a few prospective, randomized data available to adequately judge short- and long-term results of the different laparoscopic inguinal hernia techniques. A systematic review by the Cochrane Collaboration in 2005 found that among the several nonrandomized trials, TAPP was associated with an increased rate of port site herniation and visceral organ injury. This review concluded that there are insufficient data from prospective, randomized trials to make firm conclusions about the relative effectiveness of the TEP and TAPP procedures. A recent review published in 2015 studied 17,587 patients between 2009 and 2013 who underwent laparoscopic inguinal hernia repair, either TAPP or TEP. There were no differences between intraoperative complications between TAPP and TEP. However, despite a higher rate of postoperative complications in TAPP versus TEP (3.97 vs 1.70, respectively), there were no differences in the reoperation rate for complications. When the increased rate of postoperative complications was further studied, it was found that these complications were more commonly associated with larger hernia defects, scrotal hernias, and
older age, all of which were seen more commonly in the TAPP repair group. Furthermore, many reviews have shown no statistically significant differences in rates of recurrence and chronic groin pain between TAPP and TEP repair. Two studies have shown that while there are increased rates of short-term postoperative pain with TAPP, there are no differences in pain with longer follow-up (after 180 days). Thus, it can be concluded that the long-term outcomes between TAPP and TEP are comparable in terms of recurrence rate, chronic pain, and postoperative complications.

There are emerging data comparing laparoscopic techniques to open inguinal hernia repair, although the evidence is far from definitive. While there are multiple meta-analyses in the literature, only two truly compare the laparoscopic hernia technique with a tension-free open repair. A meta-analysis of 29 randomized trials in 2003 found that laparoscopic hernia repair was associated with earlier discharge from the hospital, quicker return to normal activity and work, and fewer postoperative complications than open repair. However, in these data there was a trend toward an increase in the risk of recurrence after laparoscopic repair. A separate meta-analysis reviewing 41 published randomized trials found no significant difference in risk of recurrence between the two approaches. Laparoscopic repair was associated with a quicker return to function and less postoperative pain, but also was found to have a higher risk of visceral and vascular injuries. A more recent multicenter, randomized trial that analyzed long-term hernia results in over 2000 patients in 14 Veterans Affairs hospitals found that laparoscopic hernia repair was associated with a higher recurrence rate among primary hernias, but was equivalent to open repair in recurrent hernias. In all of these studies, the laparoscopic repair was noted to take more time in the operating room. Proper laparoscopic technique also appears to play a significant role in recurrence rates. In a randomized, multicenter trial comparing 665 TEP versus 705 Lichtenstein repairs with 5-year follow-up, authors initially found that the recurrence rate following TEP (3.5%) was significantly higher \((P = 0.008)\) than that following Lichtenstein (1.2%). However, when they removed a single surgeon who was responsible for 33% of all the recurrences in the TEP group, the cumulative recurrence rate for TEP was lowered to 2.4% and was not statistically different from the Lichtenstein group. It has further been reported that there is a significant learning curve inherent in the laparoscopic approach when compared to open
Clearly, more definitive multicenter data from surgeons experienced in both procedures are needed to reach formal conclusions about the utility of both hernia approaches.

There have also been multiple studies looking at rates of chronic pain of laparoscopic versus open hernia repair. Chronic pain is one of the most common postoperative complaints after hernia surgery. A study in 2008 initially showed that TEP had increased rates of chronic testicular pain, while open repair had increased rates of impaired inguinal sensation. However, a more recent randomized controlled trial showed that TEP had lower rates of long-term postoperative pain and exercise limitations at 1 year when compared with open Lichtenstein repair.

A separate issue that deserves further study in laparoscopic hernia repair is the anatomical disturbance of the space of Retzius. This area, first described by Retzius in the 19th century, is the prevesical space located anterior and lateral to the bladder. Suprapubic prostatectomy is performed with dissection through this space, and this operation may be made more difficult following laparoscopic hernia repair.

**SURGICAL COMPLICATIONS OF GROIN HERNIA**

Although groin hernia repair is associated with excellent short- and long-term outcomes, complications of the procedure exist and must be recognized.

**Recurrence**

Recurrence of the hernia in the early postoperative setting is rare. When this does occur, it is often secondary to deep infection, undue tension on the repair, or tissue ischemia. Clearly, all of these etiologies raise the concern for a technical complication on the part of the surgeon, either in the handling of the groin tissues or the placement of mesh or suture. The patient who is overactive in the immediate postoperative setting may also be at risk for early hernia recurrence. It is thought that early exercise disrupts the suture or mesh in the repair before it has had an opportunity to hold tissue in place and promote scar tissue formation, leading to early recurrences. In the initial postoperative setting, patients may also develop seromas along the planes of
dissection as well as fluid in the obliterated hernia sac. These benign consequences of surgery must be differentiated from the more worrisome early recurrence.

Tension is an important, if not the primary, etiology of hernia recurrence. Tissues repaired under undue tension will tend to pull apart, even if sutures or mesh have been affixed to them. In addition, tension at the site of suture may lead to ischemia at the point where the suture pulls against the tissue, thereby further weakening the hernia repair. Sutures can also cut out or fall apart, especially if placed in a continuous fashion, when tensile force predominates. The role of excessive tissue tension in promotion of hernia recurrence is the basic rationale behind the modern, tension-free and increasingly suture-free hernia repairs advocated by hernia experts such as Lichtenstein and Rutkow.

The size of the hernia defect is proportional to the risk of hernia recurrence. Larger hernias have an increased rate of recurrence postoperatively. This is most likely due to the nature of the surrounding fascial tissues that are critical to the strength and reliability of the repair. As large hernias stretch and attenuate the surrounding fascial planes, these tissues are correspondingly weaker when repaired with suture or mesh. The weakened tissue may also be relatively ischemic at the time of hernia repair, although this has not been adequately studied.

An emergency operation for strangulated or incarcerated hernia may increase the risk of postoperative recurrence. This likely occurs due to the inherent inflammation, tissue ischemia, and fascial edema associated with the strangulated hernia, all of which provide an environment that causes the hernia repair to be placed through unhealthy tissue or at increased tension.

A hernia that is overlooked in the operating room also represents a potential etiology of hernia recurrence, although this should not be a major concern for the modern hernia surgeon. Most of the repairs in the current era emphasize the repair of both an indirect and direct defect through strengthening of the internal ring and inguinal canal floor, respectively.

A final etiology of hernia recurrence pertains to tobacco use and smoking. The relationship between smoking and hernia formation as well as recurrence was first reported in 1981. Further research has identified proteolytic enzymes that may degrade the connective tissue components, leading to weakened tissues and increased recurrences. 49
Infection

Infection of the hernia wound or mesh is an uncommon postoperative complication but represents another etiology of hernia recurrence. In specialized hernia practices, the incidence of wound infection following inguinal hernia operation is 1% or less. When an infection does occur, skin flora are the most likely source, and appropriate gram-positive antibiotics should be initiated. Patients who undergo mesh placement during groin herniorrhaphy are at a slightly higher risk of postoperative wound infection. It is often difficult to determine whether the mesh itself is infected or if just the skin or soft tissue anterior to the layer of mesh is infected. However, even if mesh is present, most postoperative groin hernia infections can be treated with aggressive use of antibiotics after the incision is opened and drained expeditiously. Mesh removal in the acute setting is rarely indicated. When this is mandated, primary closure or redo herniorrhaphy with a synthetic tissue substitute may be warranted and a preperitoneal approach may be necessary. Chronic mesh infections will generally present as a persistent draining sinus; these will often require mesh removal for adequate treatment.

Seromas and hematomas are frequent complications in the postoperative setting. Seromas form in the dead space remaining from a wide dissection during the hernia repair or when fluid fills the distal remnant of the hernia sac. While the sac is often ligated or excised during open herniorrhaphy, it remains in place following laparoscopic repair, and the filling of the remnant sac with seroma-type fluid has been termed a pseudohernia. This must be differentiated from the more concerning complication of the early recurrent hernia. Defined fluid collections infrequently require drainage or aspiration, as most will reabsorb or drain through the incision on their own.

Hematoma formation must be assiduously avoided during groin hernia repair. This is especially true in the anticoagulated patient, and therefore it is recommended that patients temporarily stop taking aspirin and clopidogrel at least 1 week prior to their operation. Hematoma formation may be minor, leading only to ecchymoses and wound drainage. The ecchymosis often spreads inferiorly into the scrotal plane in a dependent fashion. The hematoma usually resolves in days to weeks following repair, and supportive management for pain control, including scrotal elevation and warm packs, is all that is required. On the other hand, a large volume of hematoma is concerning, as it may serve as a nidus for infection deep in the hernia wound.
and may risk secondary infection of the prosthetic mesh. Additionally, hematoma formation following laparoscopic repair can result in a hemodynamically significant amount of blood pooling in the preperitoneal area. This is due to the fact that in laparoscopic repair, the space of dissection is more generous compared to open repairs, allowing more room for blood and fluid collections. Therefore, hemostasis at the end of a groin hernia repair is paramount to achieve effective wound healing.

**INGUINODYNIA**

Chronic groin pain following inguinal hernia repair, termed inguinodynia, is defined as pain that persists greater than 3 months following repair. There are two forms of inguinodynia: nociceptive and neuropathic. Nociceptive groin pain stems from the foreign body sensation created by mesh implantation, while neuropathic groin pain is caused by direct nerve injury during repair or delayed structural changes in the nerves resulting from inflammation created by proximity to mesh. Inguinodynia is common in varying degrees following groin herniorrhaphy. Often, neuropathic pain will follow the known dermatomal distribution of the regional nerves, including the ilioinguinal, iliohypogastric, genital branch of the genitofemoral nerve, and the lateral femorocutaneous nerves. Dermatomal mapping can be performed in the office to determine which nerves may be affected. During open hernia repair, the ilioinguinal, iliohypogastric, and the genitofemoral nerves are most commonly injured, while the lateral femorocutaneous nerve or genitofemoral trunk is more commonly injured during laparoscopic herniorrhaphy. Nerve injury is usually due to entrapment of a portion of the nerve in the mesh or suture line placed in one of the soft tissue layers but can also be caused by tacks utilized for mesh fixation during laparoscopic repair.

Neuropathic pain following open repair can be prevented by meticulously identifying all three nerves and avoiding overt manipulation of the nerves during operative dissection. This helps to preserve the investing fascial layer of the nerves and reduces their risk of harm from exposure to the mesh. The ilioinguinal and iliohypogastric nerves are generally injured during elevation of the external oblique fascial flaps or during mesh fixation, while the genitofemoral nerve is most likely to be injured during the isolation of the cord and stripping of the cremaster muscle fibers. If the nerves have been mobilized and are found to be at risk for injury to their investing fascia, they...
can then be intentionally sacrificed at time of surgery. The result of this maneuver is a region of sensory deprivation in the distributions of these nerve structures, namely, on the inner upper thigh and the hemiscrotum. However, the sensory deprivation is thought to be better tolerated by the patient than the chronic and persistent pain attributed to nerve entrapment in scar or mesh. In laparoscopic repair, nerve injury can be prevented by avoiding tack or staple placement below the iliopubic tract or in the region of the inguinal canal where the iliohypogastric and ilioinguinal nerves are susceptible to risk on the anterior side of the transversalis fascia.

Unlike neuropathic pain, nociceptive groin pain will generally not follow a dermatomal distribution. Patients will usually complain of a fullness or pressure in their groin, especially while bending over. Individuals who underwent repair with a mesh plug may be at increased risk for nociceptive groin pain due to the presence of the meshoma within the inguinal canal. CT or MRI can be obtained to help identify the presence of a meshoma, and surgery should be performed to remove the contracted piece of mesh.

Inguinodynia should first be managed conservatively, with attempts at local anesthetic injection in the affected groin. The injection of local anesthesia along the known course of a nerve serves as both a diagnostic and therapeutic maneuver. In some cases, temporary control of the chronic pain with local anesthesia may reduce or altogether eliminate the sequelae of chronic groin pain. For those who have initial but short-lived success with nerve injection, radiofrequency or nerve ablation may be attempted. When this conservative approach does not succeed, groin reexploration can be performed to ligate or excise affected nerve branches. This is clearly not the preferred first option, since the groin wound has abundant scar tissue, and previously undamaged nerve structures may be placed at additional risk. In those patients who do not fit a pattern of either neuropathic or nociceptive groin pain, surgery should be avoided as their chances of success are extremely limited. Instead they should be referred to physical therapy and a chronic pain practitioner for medical management of inguinodynia.

**Bladder Injury**

The urinary bladder may be inadvertently injured during dissection of a direct inguinal hernia sac, but only rarely during repair of an indirect defect. The bladder can also participate in a sliding hernia, so that a portion of the bladder
wall is adherent to the sac in a direct defect. Because of the potential for this complication, direct sacs should be inverted into the peritoneal cavity so that excessive dissection can be avoided. If bladder injury takes place, the sac should be opened and the bladder injury repaired in two layers using an absorbable suture. Post-repair, a urethral catheter is generally placed for a minimum of 7 to 14 days.

Testicular Injury

Testicular swelling and atrophy are seen after inguinal hernia repair. Edema of the scrotum or testis may be secondary to edema or hematoma of the inguinal canal that tracks inferomedially to the scrotum in a dependent fashion. Alternatively, a tender testicle or an atrophic testicle may be secondary to injury to the blood supply to the genitals during dissection and isolation of the cord. In most cases, this is not an emergency in the adult patient, and the testes will atrophy without significant infectious complications so that orchiectomy is rarely necessary. A testicle that is tender on examination may require ultrasonographic imaging to rule out testicular torsion or a corresponding abscess. Necrosis of the testes, a very rare complication of groin hernia repair, usually requires orchiectomy to avoid infectious complications.

In the pediatric patient, traction on the cord in the cephalad direction can cause the testes to migrate into the inguinal canal and out of the scrotum. For this reason, the scrotum is often prepped steriley in the pediatric inguinal hernia operation, and the testes is confirmed to be in appropriate position by palpation at the end of the hernia repair. If the testes remain in the inguinal canal following herniorraphy, this may require manipulation of the testes further down the canal and into the scrotum using a long atraumatic forceps or a choker instrument.

Vas Deferens Injury

Injury to the vas is a rare complication of groin hernia surgery in the male patient. Transection of the vas is the most serious form of this injury; this requires urologic consultation and likely immediate reanastomosis in the child or young adult, but may only require ligation of both ends in the older
adult patient. Minor injuries to the vas can be avoided by using gentle, atraumatic traction only and by avoiding complete grasping or squeezing of the vas. The most worrisome sequela of vas deferens obstruction or transection is the formation of antisperm antibodies in the serum, leading to infertility.

THE STRANGULATED GROIN HERNIA

The strangulation of a groin hernia is a complication of the hernia itself rather than of a hernia repair. This pathophysiologic process is associated with a high rate of morbidity and mortality, especially in the elderly population with multiple comorbidities. The risk of strangulation is highest in the first months to years after the initial presentation of a reducible hernia. Gallegos and associates estimated the probability of inguinal hernia strangulation over time to be 2.8% over 3 months and 4.5% at 2 years. It is likely that with time, the hernia contents weaken the hernia defect and widen the hernia neck so that the sac is no longer compressed as tightly, thereby decreasing the opportunity for incarceration and strangulation to take place.

The mortality from a strangulated hernia is related to the duration of the strangulation and the age of the patient. A longer duration of strangulation leads to a greater degree of tissue edema, ischemia, and risk of outright necrosis. Therefore, a strangulated hernia clearly represents a surgical emergency. The incarcerated hernia without overt signs of strangulation on examination and laboratory analysis should undergo attempts at reduction, often requiring conscious sedation to minimize discomfort. After the hernia is reduced, the repair can take place 1 to 2 days later, usually during the same inpatient hospitalization, to minimize risk of recurrent incarceration leading to strangulation.

Surgery for an incarcerated inguinal hernia is most often performed under general anesthesia given the high likelihood that bowel resection will need to be performed. Epidural or spinal anesthesia may suffice in select cases, but local anesthesia should not be employed. The location of the incision depends on the diagnosis and clinical assessment. In those patients who are unlikely to have ischemic bowel present within the hernia sac, an inguinal incision will likely be successful in both reducing the hernia contents and repairing the hernia defect. If nonviable bowel is found on exploration of the inguinal
canal, the resection and anastomosis can take place deep to the transversalis fascia in the preperitoneal space, or a midline incision can be made. If the initial physical examination yields signs of ischemic bowel that may necessitate resection, a midline laparotomy can be performed and the hernia repaired in the inguinal canal using a tissue repair after the laparotomy is closed. A helpful alternative is the preperitoneal hernia repair, which can be used to evaluate the bowel and repair the hernia defect, yet can also be easily converted to an intraperitoneal exposure if extensive bowel resection and anastomosis is required. Placement of prosthetic mesh should be avoided when possible in strangulated hernia repair given the increased risk of bacterial translocation and wound infection.

**FEMORAL HERNIA**

The femoral hernia is the second most common abdominal wall hernia, although it makes up only 5% to 10% of all hernias. The femoral hernia is more common in females than males, by a ratio of approximately 4:1.

**Anatomy and Etiology**

Figure 11-6 illustrates the anatomy of the femoral hernia. The defect through which a femoral hernia occurs is in the medial femoral canal. The anterior boundary of this defect is the inguinal ligament, the lateral boundary the femoral vein, the posterior boundary the pubic ramus and Cooper’s ligament, and the medial boundary the lacunar portion of the inguinal ligament. This space is obviously tight and does not have room to expand when hernia contents fill the sac, since the boundaries are either ligamentous, bony, or the fibrous femoral sheath and its vessels. Therefore, femoral hernias have a high propensity for incarceration and strangulation. Gallegos and associates have reported the cumulative probability of femoral hernia strangulation to be 22% in the first 3 months following diagnosis and 45% at nearly 2 years. Therefore, repair of a known femoral hernia is mandatory to avoid this highly morbid complication.
In contrast to the inguinal hernia, the femoral hernia is unlikely to be of congenital etiology. The incidence of femoral hernia in infancy and childhood is exceedingly low, around 0.5%. In addition, there is no embryologic mechanism for a preexisting sac of peritoneum in the femoral canal. The hernia defect most often presents in middle-aged to older women, suggesting that the natural loss of tissue strength and elasticity is a primary etiology.

**Clinical Presentation**

The femoral hernia often presents as a small bulge just below the medial groin crease. It is often difficult to reduce on initial presentation. The hernia usually extends caudad as the sac increases in size with abdominal contents but may extend up and over the inguinal ligament anteriorly. Not uncommonly, the femoral hernia presents acutely with strangulation given its anatomic limitations. The differential diagnosis for a femoral hernia includes femoral lymphadenopathy, groin lipoma, or a soft tissue mass of benign or rarely malignant nature.

**Treatment**
The operative approach to repairing the reducible femoral hernia differs from inguinal hernia repair in several ways. The incision is usually centered transversely just below the inguinal ligament, although a standard groin hernia incision may still afford exposure to the defect. The simplest approach is anterior to the inguinal ligament. Here, the sac can often be found, dissected, and reduced into the peritoneal cavity. Repair of the defect can be performed using a Cooper’s ligament repair as described earlier, by affixing the transversalis fascia to the Cooper’s ligament medially and the iliopubic tract laterally up to the internal ring. Alternatively, a simple suture repair can be performed by tacking the inguinal ligament anteriorly to Cooper’s ligament posteromedially to close the defect. A third option is a purse-string suture placed first anteriorly into the inguinal ligament, then through the lacunar ligament medially, the pectineal ligament posteriorly, and finally through the fascia medial to the femoral vein and back to the inguinal ligament. All of these techniques can successfully close the femoral hernia defect.

A unique complication from suture repair of the femoral hernia defect is bleeding from an aberrant obturator artery. This vessel originates from the inferior epigastric rather than the internal iliac artery and traverses a space medial to the femoral hernia defect adjacent to the pubic ramus. The medial suture placed in femoral hernia repair can injure an aberrant obturator artery if present. A simple and possibly safer way to repair the femoral defect is a mesh plug placed from cephalad to caudad to obstruct the defect and promote scar tissue formation. This technique, shown in Figure 11-7, has been reported by Lichtenstein with excellent results and low rates of recurrence.\textsuperscript{55}
If the femoral hernia sac is large and filled with voluminous intra-abdominal contents, a preperitoneal repair should be considered. In this way, the transversalis fascia is opened and the preperitoneal plane is entered. This approach is particularly useful during repair of a strangulated hernia since there is more space to allow for inspection of the bowel to ensure viability. Bowel resection, if needed, can also take place in the preperitoneal space prior to full reduction of the hernia contents.

Traditionally, femoral hernias have been repaired with an open primary suture repair. However, recently laparoscopic techniques are becoming more popular. Similar to inguinal hernias, femoral hernias can be repaired laparoscopically by a TAPP approach or a TEP repair. Both techniques are identical to the TAPP and TEP procedures for an inguinal hernia repair; in all of these repairs, the entire myopectineal orifice should be dissected out and covered with a large piece of mesh in the preperitoneal space. In addition, studies have shown that even laparoscopic approaches can be used to repair incarcerated femoral hernias safely and effectively.56

When comparing open to laparoscopic repair of femoral hernias, a large prospective cohort study in Denmark comprising over 3970 femoral hernia repairs showed that laparoscopic repair had lower risks of reoperation for a recurrent femoral hernia. The study also showed that laparoscopic repair had lower rates of developing an inguinal hernia at the incision site.57 There were no differences in the rates of chronic pain between open and laparoscopic
repair. Therefore, the procedure of choice for femora hernia repair is a laparoscopic approach.

REFERENCES


INTRODUCTION

In the 20th century the diagnosis and management of an inguinal hernia was based on the following 2 concepts: (1) all groin hernias should be repaired at diagnosis to prevent a hernia accident (defined as strangulation and/or bowel obstruction) and (2) the Bassini classical sutured repair or one of its modifications, such as the Shouldice technique, is the preferred operation by most surgeons. However, the past 25 years have seen a dramatic shift in many aspects of groin hernia management, including indications for surgery, replacement of the tissue repair with the prosthetic-based tension-free repair, and the application of laparoscopic and now robotic principles. In this chapter, we will try to emphasize some important concepts in the management of inguinal hernia as discussed by the authors and provide a different point of view in certain other areas.
Male gender, increasing age, and a family history of groin hernias are proven risk factors for groin hernias in adults.\textsuperscript{1,2} Smoking, thoracic or abdominal aortic aneurysm, history of open appendectomy, and peritoneal dialysis have also been implicated as causes of hernia.\textsuperscript{1-3} Intra-abdominal tumor, ascites, chronic obstructive pulmonary disease, chronic constipation, pregnancy, and chronic urinary retention may lead to progression. Surprisingly, the role of obesity does not seem to be as significant and may actually be protective.\textsuperscript{4,5} At the molecular level, disorders of collagen metabolism in the extracellular matrix can lead to a decreased type I (strong) to type III (weak) collagen ratio. Similarly, abnormal protein metabolism related to the matrix metalloproteinases responsible for collagen degradation and restoration can lead to connective tissue disorders such as osteogenesis imperfecta, Marfan syndrome, and Ehlers-Danlos syndrome.\textsuperscript{6-9}

Whether weight lifting is a risk factor remains controversial. A recent systematic review revealed inconclusive results about whether occasional heavy lifting, repeated heavy lifting, or a single strenuous lifting episode can lead to the development of groin hernia.\textsuperscript{10} The fact that weight lifters do not have increased incidence of inguinal hernias supports this result.\textsuperscript{4}

**PREGNANCY AND GROIN HERNIA**

Pregnant patients occasionally present with a swelling in the groin that by physical examination appears to be an obvious inguinal hernia. Before recommending surgical correction, it is imperative that varicosities of the round ligament be ruled out by ultrasound. There have been multiple case reports and small series of pregnant patients undergoing groin exploration only to find this condition.\textsuperscript{11}

**DIAGNOSIS**

None of the currently available groin hernia classification systems have been accepted as a gold standard, and differentiating a direct from indirect hernia is now more of an exercise for medical students and trainees. Imaging helps differentiate an inguinal from a femoral hernia in clinically occult hernias, but significant operator variability mars the utility of ultrasonography in these cases. Studies support the use of magnetic resonance imaging (MRI) over
ultrasonography or computed tomography (CT) scan for such occult hernias.\textsuperscript{12}

\textbf{MANAGEMENT OF INGUINAL HERNIAS}

\textbf{Watchful Waiting}

Historically, routine surgical repair soon after diagnosis has been the recommended treatment for an inguinal hernia based on the fact that managing an inguinal hernia electively is much simpler than managing a hernia accident emergently. This concept has now been challenged as randomized controlled trials have shown that patients with minimally symptomatic inguinal hernias can be safely watched and operation deferred. However, long-term follow-up studies have demonstrated that the majority of patients undergoing watchful waiting (WW) will cross over to surgery because of symptom progression. It must be emphasized that WW is not recommended for any femoral hernia because of the significant risk of hernia accident. WW is also not an option for females primarily because of the difficulty in accurately differentiating their femoral hernias from inguinal hernias by means of physical examination.\textsuperscript{13-16}

\textbf{Surgical Considerations}

\textbf{ANESTHESIA}

Despite the fact that local anesthesia is safer and results in less urinary retention, the vast majority of inguinal herniorrhaphies are performed under general or regional (epidural or spinal) anesthesia, as shown by epidemiologic data from Europe.\textsuperscript{17} Currently, regional anesthesia is felt to be the least safe and is recommended only in unusual circumstances.

\textbf{SURGICAL TECHNIQUES}

Numerous named operations for the repair of an inguinal hernia can be found in the literature, making a detailed description of all of them impractical. Indeed, over 70 named nonprosthetic tissue repairs have been described since
Bassini introduced the concept in 1887. In Table 12-1, we classify these various procedures based on the space they are performed in (anterior or preperitoneal), the type of repair (tissue or prosthetic), and whether they are conventional or robotic. Since most of the named operations are minor modifications of the established ones, representative procedures have been selected for Table 12-1 and are described in some detail below.

**TABLE 12-1: SURGICAL REPAIR TECHNIQUES FOR INGUINAL HERNIAS**

<table>
<thead>
<tr>
<th>Nonprosthetic</th>
<th>Prosthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional anterior</td>
<td></td>
</tr>
<tr>
<td>Marcy</td>
<td>Lichtenstein tension-free hemioplasty</td>
</tr>
<tr>
<td>Bassini</td>
<td>Plug and patch</td>
</tr>
<tr>
<td>Maloney darn</td>
<td></td>
</tr>
<tr>
<td>Shouldice</td>
<td></td>
</tr>
<tr>
<td>McVay repair</td>
<td></td>
</tr>
<tr>
<td>Desarda</td>
<td></td>
</tr>
<tr>
<td>Conventional preperitoneal</td>
<td>Anterior approach:</td>
</tr>
<tr>
<td>Read-Rives</td>
<td>Posterior approach:</td>
</tr>
<tr>
<td>Wantr/Stoppa/Rives (also known as giant prosthetic reinforcement of visceral sac)</td>
<td></td>
</tr>
<tr>
<td>Nyhus-Condron (iliopubic tract repair)</td>
<td></td>
</tr>
<tr>
<td>Kugel/Ugahary</td>
<td></td>
</tr>
<tr>
<td>Combined anterior and preperitoneal prosthetic</td>
<td>Bilayer prosthetic repair</td>
</tr>
<tr>
<td>Laparoscopic/robotic inguinal herniorrhaphy</td>
<td>Transabdominal preperitoneal</td>
</tr>
<tr>
<td></td>
<td>Totally extraperitoneal</td>
</tr>
</tbody>
</table>

**Anterior Repairs.** There are several steps common to all anterior repairs, whether prosthetic or nonprosthetic:

1. **Cutaneous incision:** Identification of the anterior superior iliac spine, symphysis pubis, and pubic tubercle.
2. **Incision of external oblique:** Exposure of the external oblique aponeurosis and incision through the superficial ring of the inguinal canal.
3. **Isolating the cord structures:** Lifting the cord structures from the inguinal canal at the pubic tubercle and then dissecting laterally to the deep inguinal ring, completely isolating the cord structures.
4. **Nerve disposition:** Routine division of the iliohypogastric and the ilioinguinal nerves is performed by some at this point but is not generally advised.
5. **Separation of the cremaster muscle from the sac:** The cremaster muscle is incised longitudinally for the length of the cord. If a lipoma of the cord is
found, it is removed.

6. **Isolation of the spermatic cord from the sac:** The cord should be dissected to determine if there is an indirect sac even if there is an obvious direct inguinal hernia. If an indirect sac is found, it should be ligated as proximal as possible and the distal end amputated. Many surgeons now prefer to simply reduce the sac back into the preperitoneal space, feeling that either opening or excising the sac is unnecessary.

7. **Reconstruction of the inguinal floor:** This step varies.

8. **Closure of the external oblique aponeurosis:** The external oblique aponeurosis is closed and the external ring is reconstructed.

**Conventional Anterior Nonprosthetic Repair**

**The Marcy Repair.** This simple repair is for children and adolescents. It involves high ligation of a hernia sac and narrowing of the internal ring by suturing the muscular and fascial layer to displace the cord structures laterally.

**The Bassini Repair.** Traditionally the essential step in reconstructing the inguinal floor in the Bassini operation has been that “the canal is repaired by interrupted sutures affixing the transversalis fascia medially to the inguinal ligament laterally.” Perhaps a more accurate description would be to substitute the term “triple layer (transversalis fascia, transversus abdominis muscle, and the internal oblique muscle)” for “transversalis fascia” because this step is considered the reason for the extremely low recurrence rate reported. When the procedure was exported to North America, the transversalis fascia was not opened for fear of bladder or vascular injury in favor of a “good stuff to good stuff repair,” probably accounting for the poorer results. The Bassini repair and its numerous modifications have now been shown to have a higher recurrence rate than tension-free prosthetic repairs in population-based studies and meta-analyses.\(^{19-22}\)

**The Maloney Darn.** This operation is of historical interest because it involves the use of several continuous rows of monofilament nonabsorbable polypropylene sutures between the “conjoint tendon” and the iliopubic and the inguinal ligament, in effect constructing a lattice. It is considered the precursor of the prosthetic repairs but is rarely used today.
**The Shouldice Operation.** The 4 suture line repair is now considered the gold standard tissue repair, with a comparable recurrence rate as the prosthetic repairs when performed in specialty clinics.\(^{23,24}\)

**McVay Cooper Ligament Repair.** This is a tissue repair that addresses femoral hernias. Beginning at the pubic tubercle, sutures are placed between the transversus abdominis arch and the Cooper ligament until the femoral vein is reached. The femoral canal is closed by transition sutures between the Cooper ligament and the femoral sheath. The repair is then continued laterally along inguinal ligament as in the Bassini operation. A relaxing incision in the anterior rectus sheath is always used. Increased pain and recurrence due to the tension in this repair are not uncommon.

**Desarda Repair.** This tissue repair, which is based on suturing a flap of external oblique aponeurosis to the inguinal ligament, has gained a following among certain groups of surgeons and patients.\(^{25-27}\)

**Conventional Anterior Prosthetic Repair**

**Lichtenstein’s Tension-Free Hernioplasty.** The transversalis fascia is not opened in this repair, but a large space is created beneath the external oblique aponeurosis extending from a point 2 cm medial to the pubic tubercle and extending laterally to the anterior superior iliac spine. This space is then bridged by suturing a large prosthesis (13 × 8 cm or greater) at least 2 cm medial to the pubic tubercle to the anterior rectus sheath, and then the same suture is continued in a locking fashion securing the inferior edge of the prosthesis to either side of the pubic tubercle and then the inguinal ligament and tied at the internal ring. The mesh is then slit laterally to accommodate the cord structures to create 2 tails. The wider superior tail and narrower inferior tail are tucked underneath the external oblique aponeurosis to the level of the anterior superior iliac spine with the superior tail overlapping the inferior. A single interrupted suture through the lower edge of the upper tail, the lower edge of the lower tail, and the shelving edge of the inguinal ligament creates a shutter valve around the cord, which also causes a domelike buckling effect over the direct space, thereby preventing tension in upright position. Loose interrupted sutures are used to secure the superior and medial edges to the internal oblique muscle and anterior rectus sheath,
respectively. An additional suture between the posterior surface of the mesh and the Cooper ligament is used to secure any concomitant femoral hernia.

**Plug and Patch Technique.** As mentioned by Liu and colleagues, the plug is fixed with 3 to 4 interrupted sutures and the patch positioned in a sublay technique without additional fixation. We concur completely that these mesh plugs can occasional be responsible for postherniorrhaphy groin pain and have to be explanted.

**Conventional, Preperitoneal, Nonprosthetic Repair.** The Nyhus-Condon repair was based on the importance of the iliopubic tract and is of historical interest only.

**Conventional, Preperitoneal, Prosthetic Repair.** Theoretically, intra-abdominal pressure should cause better apposition between a prosthesis and the abdominal wall because the device is on the abdominal side of the musculoaponeurotic structures of the groin, resulting in a lower recurrence rate compared to the anterior approaches. However, the recurrence rate has now become so low with any of the modern prosthetic approaches that this consideration is no longer valid.

**Anterior Approach (Read-Rives).** In this procedure, the prosthesis is placed in the preperitoneal space deep to the inferior epigastric vessels and is secured with 3 sutures placed at the pubic tubercle, at Cooper ligament, and in the psoas muscle laterally. Parietalized cord structures are then replaced over the closed transversalis fascia.

**Posterior Approach (Stoppa).** Also known as giant prosthetic reinforcement of visceral sac (GPRVS), in this approach, a large permanent prosthesis is used to reinforce the preperitoneal space over the weakened transversalis fascia, giving an extensive overlap of the Fruchaud myopectineal orifice and making the type of hernia (direct, indirect, or femoral) repaired irrelevant. Stoppa favored this approach for bilateral inguinal hernias and used a chevron-shaped prosthesis that was only secured at its superior border with 3 sutures from medial to lateral near the linea alba, semilunar line, and anterior superior iliac spine. Wantz is credited with popularizing a unilateral version.
**Kugel/Ugahary.** Kugel repair involves using a specially designed deformable prosthesis that can be inserted through a small incision made above the internal ring, which springs open in the preperitoneal space to provide a wide overlap of the myopectineal orifice. An initial version of the prosthesis was recalled because the memory recoil ring, which opens the patch after it has been inserted into the preperitoneal space, would occasionally break, resulting in serious complications such as bowel perforation. The memory ring was subsequently redesigned. Ugahary repair allows a wide overlap with mesh inserted in the preperitoneal space through a small incision kept open using special retractors.

A transrectus sheath extraperitoneal procedure (TREPP), a transinguinal preperitoneal procedure (TIPP), and the Onstep procedure are some other popular modifications, but they will not be described in detail here.  

**Combined Anterior and Preperitoneal Prosthetic Repair**

**Bilayer Prosthetic Repair.** A specially designed dumbbell-shaped bilayered prosthesis made of polypropylene is used, with one layer in the preperitoneal space to overlap the direct and indirect space as well as the Cooper ligament and the other in the conventional extraperitoneal space. It is secured with sparse interrupted sutures at the pubic tubercle, midpoint of the inguinal ligament, and internal oblique muscle. The concern with this technique is that because both the anterior and posterior spaces are violated, repair of a recurrent hernia may be compromised.

**Laparoscopic Repairs.** The laparoscopic repairs are technically more demanding, and initial results with the procedures were sometimes less than desirable. This was due to a number of technical reasons including incomplete dissection, missed hernias, insufficient size of the prosthesis or an insufficient overlap of the prosthesis over the hernia defect, mesh migration and improper fixation in cases where fixation was needed, and most importantly, a limited surgeon experience with the technique.

As experience has been gained, these problems have been solved, and the operations are increasing in frequency. This trend will probably continue as new trainees enter the market. The best indications include recurrent hernias where the preperitoneal space has not been previously dissected, bilateral hernias where the repair of both sides can be performed through the same
access sites, in association with another laparoscopic procedure performed at the same time, and in patients with sliding hernias, especially when reducible.\textsuperscript{31,32} Relative contraindications include previous surgery in the retropubic space, intra-abdominal adhesions, scrotal hernia, incarcerated inguinoscrotal hernia, and the presence of ascites. A systematic review of literature revealed that the operative time was increased with a laparoscopic repair, but less postoperative pain promoted a faster return to usual activity.\textsuperscript{33} The intraperitoneal onlay mesh (IPOM) repair, the only true minimally invasive laparoscopic groin hernia repair, is now rarely performed, which is somewhat surprising given its popularity for ventral/incisional hernia.

\textbf{Transabdominal Preperitoneal (TAPP).} The TAPP and total extraperitoneal (TEP) procedures are identical in the way the repairs are ultimately accomplished. The only difference is the method of entrance into the preperitoneal space. For the TAPP, a conventional laparoscopy is performed, and then the peritoneum is divided beginning at the medial umbilical ligament about 2 cm above the hernia defect and extending laterally in a horizontal direction toward the anterior superior iliac spine. A radical dissection of the preperitoneal space is then accomplished exposing the inferior epigastric vessels, Cooper ligament, and the symphysis pubis, reducing the direct or indirect sacs as they are encountered. It is important to adequately mobilize the inferior peritoneal flap away from the internal spermatic vessels and the vas deferens to prevent roll up of the prosthesis when the peritoneum is eventually closed. Dissection inferior to the iliopubic tract laterally should be minimized to avoid neurovascular injuries.

Indirect sacs are more difficult to deal with because of the difficulty in separating them from the cord structure, especially in chronic hernias. A large inguinoscrotal sac does not need to be removed in its entirety and can be divided at a convenient point along the cord structures with the proximal side ligated and the distal side left widely opened to avoid the excessive incidence of hydrocele and vascular disruption in the distal cord that could lead to various testicular complications. The robotic modification of this technique is becoming increasingly popular. In addition to the improved 3-dimensional optics, because manipulations are made at the tips of the robotic instruments, there is less torqueing at the laparoscopic cannula sites, which might translate into less pain.

Most surgeons now prefer a larger prosthesis and fewer fixations with
tacks to lessen postoperative pain. Care should be taken to avoid the Triangle of Doom (site of femoral vessels medially inferior to the iliopubic tract) and the Triangle of Pain (site of lateral cutaneous nerve of thigh or branches of genitofemoral nerves laterally inferior to the iliopubic tract).

**Total Extraperitoneal (TEP).** An incision is made at the umbilicus, as if one were planning to perform open laparoscopy. The rectus sheath is opened on one side, and the rectus muscle is retracted laterally. Blunt dissection is then begun in the space between the rectus muscle and the posterior rectus sheath with or without the use of a dissecting balloon. Once the space is large enough, 2 additional cannulas are placed in the midline, one approximately 5 cm above the symphysis pubis and the other midway between the umbilicus and the symphysis pubis. The dissection of the preperitoneal space is completed under direct vision. The rest of the procedure is identical to the TAPP. Although literature generally favors TEP over TAPP for avoiding the complications associated with entering the peritoneal cavity, including visceral or vascular injury, adhesion formation, and trocar site hernias, there are insufficient data to conclude whether TAPP or TEP is superior. The choice is largely based on the surgeon’s comfort level and background training.\(^34,35\)

**Sports Hernias**

The term *sports hernia* is confusing because, by definition, although presenting with typical symptoms of an inguinal hernia, patients with this condition do not have a hernia either by physical examination or imaging studies; hence, a much better term is *athletic pubalgia*. The exact pathogenesis is more a matter of speculation than fact, but most agree that shear force across the pubis leads to stretching or tearing of the rectus muscle and/or the musculoaponeurotic structures that make up the inguinal canal.\(^36\) It should be treated surgically only after all attempts at conservative management with analgesics and anti-inflammatory medications, physical therapy, and core strengthening exercises have failed.

Operations similar to a Bassini anterior approach without mesh, involving tightening various attachments around the pubis through imbrication of the inguinal floor to the inferolateral border of the rectus abdominis, pubis, and inguinal ligament and reattachment of the inferolateral edge of the rectus
abdominis muscle to the fascia of the pubis and anterior ligaments, have been recommended. A prospective cohort study has reported excellent results with earlier return to sporting activity with a laparoscopic preperitoneal operation with mesh. This has also been reported in other smaller series. However, many authorities question these results because the preperitoneal approach does not address the basic pathology, which is disruption of the attachments noted earlier.

REFERENCES


INTRODUCTION

The term hernia is used to describe a weakness or defect of the abdominal wall, through which abdominal contents can protrude. It is important to note the distinction between the hernia defect and hernia contents, as surgical repair is generally more concerned with the former, with a few exceptions. Abdominal wall defects arise at areas of weakness in the abdominal wall. These areas include sites of previous surgery, the umbilicus, as well as areas of weakened abdominal and/or flank musculature such as in lumbar hernias.¹

Patients may unknowingly have an abdominal wall or fascial defect that only becomes apparent after intraabdominal or preperitoneal contents pass through the hernia defect. This is especially true of umbilical hernias, which are the most common type of ventral abdominal hernia.²
UMBILICAL HERNIA

The umbilicus is a natural area of weakness in the anterior abdominal wall. Located in the linea alba, it is technically a scar, located at the point of passage of the umbilical vessels through the abdominal wall while in utero. The fascial edges of the hernia develop by the third week of gestation, with the umbilical cord developing by week five. The extra-abdominal rotation of the intestine occurs between the sixth and tenth weeks of gestation, with fascial defect fusing thereafter. A hernia occurs after this area fails to close or later stretches and reopens as an adult. These hernias have been documented as early as the ancient Egyptians, with the first known repair occurring in the first century AD by Celsus. The first series of primary suture repairs were reported by Mayo in 1901, a technique that largely remains consistent today for small defects.

Incidence

A wide estimated range of neonatal incidence exists for umbilical hernias. In Caucasian babies, the reported incidence is 10% to 30%. For unknown reasons, the incidence in African-American children is higher. Prematurity and family history of umbilical hernia are known risk factors.

The vast majority of congenital umbilical defects close as infants grow into early childhood. In fact, once children are entering school age, only about 10% of previously diagnosed defects remain on physical exam. For this reason, most pediatric surgeons recommend deferring repair for uncomplicated umbilical defects. The current recommended age for surgical repair in the pediatric literature is at least 2 to 3 years, with many surgeons advocating for even later.

Umbilical hernias diagnosed in adulthood tend to be acquired in nature, and therefore it is more difficult to establish a true incidence. A female predominance exists, with a female:male ratio of 3:1. Also, medical comorbidities or physiologic factors that increase intraabdominal pressure confer a higher incidence of umbilical hernia. These include pregnancy, obesity, abdominal ascites, chronic obstructive pulmonary disease, or persistent bowel distension or obstruction. In the adult patient, hernia formation seems to be the result of repeated stress on an already vulnerable
Clinical Manifestations

An umbilical hernia is typically not difficult to diagnose, and the list of differential diagnoses is short. On physical exam, the practitioner will appreciate a soft mass overlying or adjacent to the umbilicus. Most hernias are reducible and contain only preperitoneal fat or omentum, although some may contain bowel, and caution should be exercised when attempting reduction. In most cases, the fascial defect can be palpated and the defect size estimated. While uncommon, other conditions at the umbilicus may mimic a hernia; an abdominal wall varix, granuloma, or peritoneal tumor implant (Sister Mary Joseph’s nodule) all can be misdiagnosed as an umbilical hernia.

Most umbilical defects do not warrant surgical repair since the majority are small and asymptomatic. However, if the defect is causing discomfort, increasing in size, obstructing bowel, or compromising the overlying skin, surgery is indicated. Many patients will request repair upon hearing they have a previously unknown hernia; in these cases, the patient should be counseled appropriately by an experienced surgeon.

Umbilical hernias secondary to chronic liver failure and ascites represent a special circumstance. First, any Childs classification confers a higher risk of postoperative mortality and morbidity. Second, in this patient population, the risk of hernia recurrence is significantly elevated. Furthermore, the risk of prosthetic mesh infection, if used, is higher. For these reasons, surgical repair in these patients should be reserved for cases of acute incarceration or progressively symptomatic hernias. These patients should have an explanation of the full spectrum of surgical risk prior to deciding on a treatment.

Treatment

In the patient with a small umbilical hernia, a short curvilinear incision is made just inferior to the umbilicus. Dissection is carried through the subcutaneous tissues and down to the fascial level. The neck of the sac is then encircled with a hemostat. After the sac is dissected free of its umbilical skin attachments, it can be reduced or inverted completely into the peritoneal area.
cavity or incised to explore the contents of the hernia sac. In this way, the redundant portion of the sac can be excised using electrocautery. The fascial defect is then closed transversely with interrupted sutures in an interrupted, figure-of-eight, or horizontal mattress fashion. The skin of the umbilicus is tacked to the fascia layer using a single absorbable suture. This operation is usually performed under local, local with sedation, or general anesthesia depending on patient factors and the size/morphology of the defect. The traditional “vest-over-pants” technique originated by Mayo is less commonly utilized since overlapping fascial closures have been shown to weaken the overall wound strength in hernia repair.

In large defects where fascial reapproximation results in significant tension, a prosthetic mesh may be used. Mesh cones were used in the past but are generally not recommended currently due to risk of migration and recurrent hernia. Composite meshes that are made with protective bioabsorbable layers allow for the mesh to be placed as an underlay in the peritoneal cavity with significant, usually 4 to 5 cm, fascial overlap in all directions. An overlay mesh with uncoated synthetic mesh is also an option to help reinforce the fascial closure. The techniques utilizing prosthetic mesh, including retrorectus and preperitoneal mesh placement, are described in more detail later in the chapter.

INCISIONAL HERNIA

Incidence

Incisional hernias have been reported in 10% to 20% of patients following laparotomy, with at least one-third of these patients presenting 5 to 10 years postoperatively. It is estimated that over 100,000 incisional hernia repairs are performed in the United States alone. Unsurprisingly, the rate of incisional hernias is lower following minimally invasive surgeries. Recent data have suggested the means of fascial closure following laparotomy greatly influences the rate of incisional hernia repair, with the traditional “1 cm bite, 1 cm travel” producing higher levels of tissue ischemia than a “small, frequent bite” technique. This technique also limits the degree of fascial disruption during normal patient motion. Transverse laparotomies, although rarely performed in the adult population, may also protect against
incisional hernia, possibly due to the two-layer fascial closure and the robust vascularity of the rectus muscles.\textsuperscript{11,12}

Multiple risk factors for incisional hernia have been identified, including obesity, wound infection, diabetes, smoking, immunosuppression medication, ascites, advanced age, and poor nutritional status. Many of these factors predispose to an environment of relative ischemia or deficiency in macromolecules necessary for wound healing. Wound infection has the strongest association with a subsequent hernia, and as such, most surgeons advocate for early reopening and drainage of infected surgical wounds to improve healing.\textsuperscript{13–16}

Normal wound healing produces long-term collagen deposition and remodeling that maintain the strength of the scar. However, the resulting mature scar is only 80% as strong as the native presurgical fascia. Thus, every surgical wound represents an area of relative weakness that can be exacerbated over time with repeated strain.

**Clinical Manifestations**

Most patients with an incisional hernia will present with a palpable bulge underlying a previous abdominal incision.\textsuperscript{7} The hernia may present with varying degrees of discomfort. Occasionally, the patient may also voice cosmetic concerns as the hernia becomes increasingly protuberant. Some patients may present acutely with an incarcerated hernia or symptoms of a bowel obstruction such as nausea, vomiting, or obstipation. Less commonly, the overlying skin may be subject to an increasing degree of pressure secondary to the hernia, possibly compromising the dermal vascular plexus leading to “paper thin” skin or skin erosion.

On physical examination, the hernia sac should be palpable, and depending on morphology, an attempt should be made to approximate the fascial edges. Examination can be significantly impaired by an obese body habitus. It is especially important to examine the entirety of the abdominal wall, especially along the same incision, to identify other occult defects which are often present.

Extremely large incisional hernias may present with a large proportion (25% or more) of the abdominal viscera within the hernia sac, a condition commonly referred to as “loss of domain.”\textsuperscript{17,18} These hernias typically have a
fascial defect greater than 10 cm in diameter. Multiple physiologic changes occur in these patients as a result, most notably musculoskeletal, alimentary, and pulmonary dysfunction. The position of the bowel within the hernia sac leads to chronic venous and lymphatic congestion as well as chronic bowel dilation. Over time this leads to bowel thickening, congestion, and dysfunction. The weight of the hernia sac coupled with the disruption of the abdominal core muscles also predisposes to a hyperlordosis of the lumbar spine that can lead to chronic back pain. Lastly, the drop in intraabdominal pressure that results following extra-abdominal migration into the hernia sac alters the normal pulmonary mechanics and physiologic pressures that drive respiration. Many of these patients require intensive pulmonary care.

**Treatment**

The treatment of ventral hernias has undergone significant changes in the past 20 years, driven by advances in technology, materials, and “rediscovered” surgical techniques such as the classic retrorectus repair popularized by Rives and Stoppa.

**MESH SELECTION**

Incisional hernias are, by definition, areas of poor fascial healing and weakness. Therefore, for most clean cases, prosthetic mesh is recommended. The material used will ultimately depend on the location of mesh implantation and the degree of possible contamination. For example, synthetic polypropylene should not be used in the peritoneal cavity due to the risk of fistulization or adhesion to the bowel. Also, permanent synthetic mesh, at this time, is not recommended in contaminated cases.

Biologic meshes have been used in contaminated fields as an alternative to synthetic mesh. However, current data show higher rates of wound complications and hernia recurrence with biologic mesh compared to synthetic mesh. Biologic meshes also carry greatly increased material cost. Absorbable mesh, such as Vicryl, is a much cheaper temporary solution in contaminated fields.

Synthetic meshes are available in a variety of materials, sizes, and weight. The most commonly used materials are polypropylene, polyester, and ePTFE. Large-pore mesh offers decreased surface area to harbor infection but retains
significant strength. Recent data have shown acceptable rates of mesh infection, about 6%, when lightweight, macroporous polypropylene was used in clean-contaminated fields, although this remains controversial. Composite synthetic meshes are also offered with a protective visceral coating that allows safe placement in the peritoneal cavity.19–21

**MESH LOCATION**

The various positions for mesh placement are listed in Table 13-1.5 The common theme underlying mesh placement is complete defect coverage with wide fascial overlap. Intraperitoneal placement is performed easily but suffers from high rates of mesh migration, and due to decreased tissue ingrowth, higher mesh infection rates. Preperitoneal and retrorectus positioning benefits from the increased vascularity of their respective spaces, as well as decreased fixation requirement, but requires more dissection to perform. Onlay mesh placement requires the elevation of lipocutaneous flaps and has higher rates of surgical site occurrences, but has experienced a resurgence in recent years as it is best suited for uncommon hernia sites such as the flank.

**TABLE 13-1: MESH POSITIONING**

<table>
<thead>
<tr>
<th>Mesh Position Nomenclature</th>
<th>Anatomic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onlay</td>
<td>Anterior to anterior rectus fascia</td>
</tr>
<tr>
<td>Retrorectus/sublay</td>
<td>Posterior to rectus abdominis muscle/</td>
</tr>
<tr>
<td></td>
<td>anterior to posterior rectus fascia</td>
</tr>
<tr>
<td>Preperitoneal</td>
<td>Posterior to posterior rectus fascia/</td>
</tr>
<tr>
<td></td>
<td>anterior to peritoneum</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Posterior to peritoneum</td>
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</table>

Most laparoscopic repairs involve intraperitoneal onlay mesh (IPOM) placement, with good results. However, increasing numbers of surgeons have begun to use minimally invasive techniques to place mesh in the preperitoneal or retrorectus position.
OPEN REPAIR—UNDERLAY

The traditional open repair, using prosthetic mesh, utilizes an overlay mesh position with multiple points of transfascial fixation with nonabsorbable sutures. An incision should be made in the previous abdominal scar (excising the scar, if necessary) and dissecting down to the hernia sac. Great care should be taken when entering the hernia sac, as abdominal viscera might be adhered to the parietal peritoneum. Once the peritoneal cavity is entered, all intraabdominal adhesions should be mobilized at least 5 cm away from the fascia defect.

A mesh approved for intraperitoneal placement, such as composite meshes or ePTFE, should be selected and appropriately sized for the defect, allowing for at least 4 cm fascial overlap on all sides. The mesh should be secured to the fascia using several interrupted nonabsorbable sutures around the perimeter of the mesh. Once all sutures are placed, the mesh should be significantly taut so that defect closure, if feasible, does not produce inappropriate laxity in the prosthetic. If fascial closure is not possible, it is important for the mesh to be taut so as not to produce a “pseudorecurrence” of a bulging prosthetic through the open hernia defect.

Multiple layers of tissue, including Scarpa’s fascia and subcutaneous fat, should be closed over the mesh to help protect the prosthetic from infection.

OPEN REPAIR—RETRORECTUS

The classically described retrorectus repair was independently developed by Jean Rives and Rene Stoppa in the 1960s. While technically more demanding, the repair benefitted from a two-layer fascia closure as well as placement of the prosthesis within the highly vascular retrorectus space, which promotes more robust tissue ingrown in the mesh and protection from infection. This technique was initially abandoned by minimally invasive surgeons with the rise of intraperitoneal onlay mesh placement, but the more recent growth in robotic surgery has led to the adoption of retrorectus dissection using minimally invasive techniques.

The abdomen is entered in a similar fashion as for the onlay technique. However, it is also possible to accomplish the dissection without violating the peritoneal cavity at all. The medial edge of the rectus sheath is identified and incised, and this incision is extended along the length of the hernia defect.
The rectus abdominis muscle should then be easily identified and its fibers bluntly swept anteriorly. This plane should be developed laterally to the lateral border of the rectus sheath, taking care not to injure the neurovascular bundles penetrating the muscle. Once this dissection is completed on both sides of the defect, the two sides are connected in the upper and lower midline. The posterior fascia can then be closed using a running absorbable suture. An uncoated medium-weight mesh is then selected and sized to fit on top of the posterior closure. Although no fixation is absolutely necessary, if such fixation is desired, transfascial nonabsorbable sutures can be secured to the mesh and brought through the anterior sheath. Once the mesh is in place, the anterior sheath is then closed using either permanent or slowly-absorbing suture.

ANTERIOR COMPONENT SEPARATION

“Separation of components” was first described by Ramirez in 1990 as a method for increasing laxity of the abdominal fascia to achieve tension-free midline closure. The original description of the technique did not include the use of mesh. However, since then, the component separation has been coupled with underlay mesh or the retrorectus technique to allow for midline closure along with prosthetic reinforcement.

To start the procedure, the anterior fascia is identified and secured. The plane between the anterior fascia and the subcutaneous tissues is then incised and large lipocutaneous flaps are developed. This is continued lateral to the rectus sheath. The lateral border of the rectus sheath is then manually identified and a superficial fascial incision is made 1 to 2 cm lateral to the rectus sheath. This incision should only divide the external oblique aponeurosis. Once in this space, a clamp can be used to assist in extending the division the entire craniocaudal length of the hernia defect. The procedure should then be completed on the opposite side.

With the anterior component separation, the surgeon can achieve up to 10 cm of fascial advancement on each side. However, the creation of large lipocutaneous flaps does predispose the patient to wound complications such as seroma, abscess, and skin necrosis. Most centers consider active tobacco use an absolute contraindication, and most require a hemoglobin A1c less than 7.
POSTERIOR COMPONENT SEPARATION

The posterior component separation, or transversus abdominis release (TAR), was developed by Yuri Novitsky and Michael Rosen as a solution to the wound morbidity and mesh limitations of the anterior component technique. The technique creates an “extension” of the retrorectus plane developed in the Rives–Stoppa repair, allowing for mesh placement posterolateral to the psoas muscle as well as creating fascial advancement by releasing the attachment of the transversus abdominis muscle.

Once the retrorectus space has been developed in the previously described Rives–Stoppa repair, the posterior lamella of the internal oblique aponeurosis (above the arcuate line) is then incised approximately 1 cm medial to the neurovascular bundles along the length of the hernia to expose the transversus abdominis muscle fibers. These fibers are divided superiorly and inferiorly to then enter the preperitoneal space. This plane can then be bluntly developed by sweeping the transversus abdominis fibers laterally to create an appropriately-sized mesh pocket. Any holes in the peritoneum or fascia should be closed with absorbable suture.

The posterior fascia is then closed at the midline using a running absorbable suture. After the prosthetic mesh is placed, it can be fixed using transfascial sutures, biologic glue, or nothing at all. The anterior fascia is then closed over the mesh using running suture. Some practitioners advocate for the placement of drains within the retrorectus space, although their utility and safety have been questioned.

LAPAROSCOPIC INTRAPERITONEAL REPAIR

The first laparoscopic ventral hernia repair was described in 1993 and utilized ePTFE fixed to the abdominal wall with staples. Since then, while the basic technique has not significantly changed, multiple advances have been made with mesh materials and fixation techniques.

In order to repair midline defects, the abdomen is typically accessed through lateral ports on the right or left side of the abdomen. The abdominal wall is then completely cleared of all adhesions in the area of the hernia repair. The defect is then measured and an appropriately sized mesh is selected to allow for at least 4 cm of fascial overlap post-repair. The selected mesh must be safe for contact with abdominal viscera. Composite meshes or
ePTFE are all suitable but each material has its own set of drawbacks and limitations. While many fixation techniques have been used, we believe that a moderate amount of transfascial fixation is necessary to prevent mesh migration. It is important to note that the peritoneum is a mobile structure lacking in tensile strength, and should not be relied upon for permanent mesh fixation.

At least four nonabsorbable sutures should be preplaced at the cardinal points of the mesh prior to insertion into the abdomen. Once in the abdomen, the mesh should be unfurled and each transfascial suture should be brought out through a small skin incision or puncture using a suture passer. Once all sutures are in place, the mesh can then be “parachuted” up to the abdominal wall and tied down to the fascia. A “double ring” or “double crown” of tacks can then be used to flatten the mesh against the wall and eliminate any gaps along the edge.

Closure of the defect prior to mesh insertion is preferable, although not required. Current data show that primary closure does not affect recurrence rates but may reduce postoperative seroma formation.

**SPIGELIAN HERNIA**

A Spigelian hernia occurs along the linea semilunaris, where the aponeuroses of the oblique and transversus abdominis muscles fuse just lateral to the rectus sheath. Spieghel originally described this fascia as a zone of transition between the posterior rectus sheath and the lateral abdominal wall musculature. The linea semilunaris varies in width along its craniocaudal extent, becoming widest where it intersects the arcuate line just below the level of the umbilicus. Because of this widening, Spigelian hernias occur more frequently (~90%) at this location where the fascia may be more attenuated (Fig. 13-1). Spigelian hernias in the upper abdomen are rare and typically represent mislabeled lateral incisional hernias.
In the most common types of Spigelian hernias, the external oblique aponeurosis remains intact with an underlying posterior defect. This is because the anterior sheath undergoes little anatomic rearrangement at the arcuate line, in contrast to the posterior fascia. As a result, a combination of preperitoneal or intraabdominal contents may protrude through the deepest layers of abdominal fascia but not completely into the subcutaneous space. This may have diagnostic implications to be discussed later. However, a rare subset of Spigelian hernias may in fact penetrate through all layers of the abdominal wall (Fig. 13-2).
FIGURE 13-2 The Spigelian hernia. A. Breaching the Spigelian fascia. B. The most common type has passed through the transversus abdominis and the internal oblique aponeuroses and is spreading out in the interstitial layer posterior to the external oblique aponeurosis. C. The less common type in the interstitial layer between the transversus abdominis aponeurosis and the
internal oblique muscle. D. The least common subcutaneous type.

**Incidence**

True Spigelian hernias are well described but not common. Over 1000 cases have been reported in the surgical literature, but the true incidence is difficult to ascertain due to difficulties in diagnosis and frequent mislabeling of incisional hernias (such as trocar site hernias). True Spigelian hernias have been estimated to constitute less than 1% of all abdominal wall hernias, with a slight female predisposition.

**Clinical Manifestations**

The physical exam of a Spigelian hernia may reveal a vague fullness or lump just lateral to the rectus muscle. Due to a likely intact external oblique fascia, the examiner may not be able to feel the edges of a defined fascial defect. Depending on symptomatology, the area may be tender to manipulation. It should be noted that about 20% of Spigelian hernias present with acute incarceration. As with all hernias, patients with connective tissue disorders, diabetes, smoking history, or history of trauma to the area are more likely to develop Spigelian hernias, although the low incidence makes study of patient demographics difficult.

Diagnosis is greatly aided by imaging modalities. Ultrasound offers a cheap first-line modality that allows the examiner to visualize the abdominal fascia layers. Computed tomography is also easily obtainable in most centers. It allows the practitioner to visualize the entire abdominal wall to plan for repair, but does expose the patient to ionizing radiation.

**Treatment**

Spigelian hernias should be repaired due to their higher risk of incarceration and vague physical diagnosis. Surgical repair can be performed via open or minimally invasive techniques. There are little data on the benefits of prosthetic mesh in these hernias due to their rarity. However, for moderately-sized defects (>2 cm) we recommend prosthetic reinforcement in open and minimally invasive cases.37–39
Open repair involves a direct cutdown (typically transverse) overlying the hernia and the opening of the external oblique fascia to expose the posterior wall defect. The surgeon can then utilize a sublay technique or place the mesh anterior to the posterior fascia following primary closure. The external fascia is then closed primarily.

Minimally invasive repair is most commonly performed transabdominally but may also be attempted extraperitoneally by accessing the space of Retzius. If approaching the repair from the peritoneal cavity, an IPOM may be placed. Alternatively, a peritoneal flap can be created with development of the preperitoneal space and reduction of the hernia sac prior to the insertion of mesh. If placing mesh in the preperitoneal space, a coated, or composite, mesh is not necessary.

LUMBAR HERNIA

The lumbar region is bordered by the 12th rib superiorly, the iliac crest inferiorly, erector spinae muscles posteriorly, and the line between the tip of the 12th rib and anterior superior iliac spine (ASIS) anteriorly. Within this region, muscle groups run obliquely, and it is this “criss-crossing” of muscles that creates two potential triangles for hernia formation. The triangle of Petit is more inferior and is bordered by posterior edge of the external oblique muscle anteriorly, the anterior edge of the latissimus dorsi posteriorly, and the iliac crest inferiorly. Hernias through Petit’s triangle are more common than those through Grynfeltt’s triangle. The triangle of Grynfeltt, more superior than Petit, is bordered by the 12th rib, the serratus posterior inferior muscle, the posterior border of the internal oblique, and by the quadratus lumborum and erector spinae muscles (Fig. 13-3).
Incidence

Lumbar hernias are well-recognized but rare, occurring most commonly in patients over 50 years in age. There is a slight male predominance, as well as a slightly higher incidence of left-sided hernias. These hernias are most commonly acquired rather than congenital, occurring after surgical access or trauma.

Clinical Manifestations

Lumbar hernias may present as a palpable mass or lump in the lumbar space. Patients may complain of discomfort or changes in size. Due to the complex anatomy of the retroperitoneum, most lumbar hernias do not contain bowel but may contain fat, or in severe cases, retroperitoneal organs such as the kidneys. Lumbar hernias rarely cause strangulation due to the absence of rigid fascia and the relative pliability of muscle. Most of these hernias are diagnosed by CT scan.
Treatment

Once discovered, surgical repair should be offered to patients with symptomatic hernias. Repair may be attempted via open or minimally invasive methods. Each repair should involve the patient positioned in the lateral decubitus position.

Open repair involves a direct cutdown over the hernia and dissection to the lumbar musculature. Once the defect has been identified, the hernia sac should be completely reduced under the musculature. If the defect is small, it can be reapproximated using multiple interrupted nonabsorbable sutures. However, in larger defects, the plane underlying the lumbar musculature should be developed and a prosthetic mesh placed with ample (4 cm) overlap. While mesh fixation is not required, especially if the overlying muscles are subsequently reapproximated, multiple absorbable sutures may be placed. An alternative to the sublay mesh technique is the overlay position, which involves the muscle closure followed by mesh reinforcement, fixated with multiple nonabsorbable sutures.

The repair of lumbar hernias through minimally invasive techniques most commonly requires peritoneal access. The lumbar space can be developed by first incising the peritoneal reflection tethering either the right or left colon. Once in this space, dissection can be continued to the psoas muscle posteriorly. Once the defect is identified and the hernia sac reduced, the muscle edges should be brought together with nonabsorbable suture and an uncoated mesh can be placed with minimal fixation. The peritoneal flap is then closed with suture or tacks.

**EPIGASTRIC HERNIA**

An epigastric hernia is a defect between the umbilicus and xiphoid process in the midline of the abdomen. The entity was first described in 1285 by Villeneuve, but not until 1802 was a successful repair performed, by Maunior. These defects are typically elliptical in shape and oriented horizontally. It is believed that these defects are more acquired in nature rather than congenital, since they are rare in children. Previous surgery, trauma, or repeated straining and/or intraabdominal pressure have all been implicated in their formation.
Incidence

The estimated incidence of epigastric hernias in the United States is between 2% and 3%, with a male-to-female ratio of 3:1. These hernias are more likely to present in middle age and are relatively rare in children.

Clinical Manifestations

The epigastric hernia presents similarly to other ventral or incisional hernias. The patient may complain of a symptomatic bulge in the upper abdomen. In contrast with more inferior defects, epigastric hernias are less likely to contain bowel. Rather, they are more likely to contain omentum or preperitoneal fat. For this reason, epigastric hernias are often missed on laparoscopy due to the lack of a peritoneal hernia sac. The examining clinician should assess for reducibility, tenderness, and any change in size or morphology from previous examinations.

Treatment

The treatment of epigastric hernias is essentially the same as other ventral abdominal wall hernias. For smaller hernias, typically less than 2 cm, a primary suture repair may be an acceptable option. However, for larger defects, a prosthetic mesh should be placed to achieve a lower recurrence risk.

The placement of mesh in the upper abdomen is often complicated by limits on mesh fixation. For subxiphoid defects, the falciform ligament often obstructs mesh placement. Furthermore, transfascial fixation is not feasible above the costal margin. Therefore, for epigastric defects where the proximity to the costal margin limits adequate mesh overlap on the superior margin, we recommend a laparoscopic repair with the placement of a preperitoneal mesh. This peritoneal flap may be extended onto the diaphragm, and mesh positioning can be completed with minimal fixation. Following the mesh placement, the peritoneal flap is then closed with absorbable suture or tacks. If mesh overlap along the superior aspect is not a concern, a laparoscopic IPOM procedure may also be performed after dividing the falciform ligament to facilitate mesh placement.
REFERENCES


INTRODUCTION

Incisional hernias are a common complication of midline laparotomies, with a reported incidence of 9% to 20%.\textsuperscript{1} Over 100,000 incisional hernia repairs are performed annually in the United States alone.\textsuperscript{2} Since the introduction of laparoscopic incisional hernia repair (LIHR) by LeBlanc in 1993, the approach has gained popularity with general surgeons as a preferred technique for selected incisional hernia repairs.\textsuperscript{3}

As LIHR becomes more common in the armamentarium of general surgeons, more information has become available regarding the benefits of laparoscopic hernia repair. However, only a small number of randomized trials exist comparing open hernia repair to laparoscopic repair. These studies have mixed results, with no clear consensus proving that one should replace
the other as a standard approach to incisional hernias. Thus, it is important for
general surgeons to be familiar with both techniques of hernia repair, as well
as risks and benefits of both. This chapter will focus on the advantages and
disadvantages of LIHR, discuss technical considerations, and review the
literature on outcomes.

ADVANTAGES OF LAPAROSCOPIC VENTRAL
HERNIA REPAIR

Early studies demonstrated a decrease in wound complications, hospital stay,
operative times, and recurrence rates with LIHR compared to open primary
repair.\textsuperscript{4,5} However, more recent studies have found decreased wound
complications and length of hospital stay with LIHR, with no difference in
recurrence rates.\textsuperscript{6-8} The smaller incisions used for the laparoscopic approach
are thought to be the major factor leading to decreased wound complications.
Studies have demonstrated a decreased rate of surgical site infection in
laparoscopic versus open incisional hernia repair (2.3\% vs 9.2\%,
respectively),\textsuperscript{9} including superficial and deep surgical site infections as well
as wound disruption.\textsuperscript{10} Large tissue flaps are not raised during LIHR, thereby
obviating the need for postoperative surgical drains and further decreasing
the risk of wound complications. In contrast to the known benefits of
laparoscopic approach for other surgeries, it was thought that the smaller
incisions used in LIHR would result in less postoperative pain than open
repair. However, recent studies demonstrate either an increase or no
difference in early postoperative pain compared to open procedures.\textsuperscript{7}

DISADVANTAGES OF LAPAROSCOPIC
INCISIONAL HERNIA REPAIR

One of the most feared complications of LIHR is an intestinal injury.
Enterotomies can occur during initial trocar placement, lysis of adhesions,
and intestinal manipulation. Laparoscopic adhesiolysis has been associated
with an increased risk of unrecognized bowel injuries compared to open
techniques.\textsuperscript{6,11} The incidence of enterotomy has been reported as 7.9\% for
laparoscopic repair compared to 7.3\% for open repair.\textsuperscript{12} Injuries most
commonly occur in the small intestine. A missed intestinal injury can have harmful effects, including mesh infection, sepsis, and even death. The mortality of an unrecognized injury is 7.7%, compared to 1.7% for an injury recognized intraoperatively.\textsuperscript{11} If recognized at the time of surgery, it is at the discretion of the surgeon to attempt laparoscopic repair or convert to an open procedure. If recognized in the postoperative period, operative management with intestinal repair, source control, and removal of the mesh is typically mandated.

Most hernia defects are not reapproximated with the laparoscopic technique, causing patients to potentially have a persistent bulge after laparoscopic repair. Often, this is confused with a recurrent hernia, and patients should be counseled appropriately. It also leaves a dead space, which can increase the risk of developing a postoperative seroma. Most seromas can be observed without intervention; however, symptomatic ones may require percutaneous drainage. Again, patients should be advised that they may have a persistent mass following laparoscopic repair that decreases in size and usually disappears over time. The risk of seroma formation can be decreased by placement of a compressive abdominal binder.

\textbf{PATIENT SELECTION}

Identifying appropriate patients for the laparoscopic approach includes determining the size of the defect, the ability to get lateral to the defect, adequate tissue for mesh fixation, extent of prior surgical procedures, and experience of the surgeon. Novice surgeons should select low-risk hernias for their initial procedures. These would include small, uncomplicated, reducible, midline, periumbilical hernias with healthy overlying skin and no prior history of peritonitis. With increased experience, surgeons can extend the laparoscopic approach to more complicated presentations, but even the most experienced surgeons would not choose a laparoscopic approach for patients with open skin lesions, fistulas, or massive loss of domain.

\textbf{TECHNICAL CONSIDERATIONS}

Care is taken when selecting the method of entry for the initial placement of the trocars. Consideration must be given to the location of the hernia to be
repaired as well as previous surgical procedures and incisions. For instance, if the patient had a right colectomy via a midline incision, then initial trocar placement should be on the left side of the abdomen to avoid potential adhesions related to the right-sided dissection. The trocars should be placed laterally at least 5 cm from the nearest fascial defect. The contents of the hernia sac should be carefully reduced and adhesiolysis carried out using blunt or sharp techniques. To avoid delayed perforation, energy devices are used sparingly and only when no intestine appears to be involved. It is essential to inspect the reduced contents to assess for intestinal injury before proceeding to mesh placement. The abdomen should be carefully examined to avoid missing any hernia defects as this can increase the risk of recurrence.

The use of synthetic mesh in open incisional hernia repair has been demonstrated to decrease the recurrence rate when compared to primary repair. Laparoscopic primary repair without mesh has been described; however, there is a paucity of data to support its routine use.\textsuperscript{13,14} Incorporating synthetic mesh in LIHR is considered a standard of care and is used in most laparoscopic repairs. The type of mesh chosen is based on the surgeon’s preference, but certain considerations should be made when making a selection. The location of the mesh will be intraperitoneal; as such, it will be in contact with visceral surfaces. Dual-sided meshes were created for the purpose of allowing appropriate tissue ingrowth on the peritoneal surface and preventing adhesion formation on the visceral surface. The types of mesh and materials available are beyond the scope of this chapter and constantly evolving; however, surgeons performing LIHR should be familiar with mesh approved for use in the abdominal cavity.\textsuperscript{15} Once identified, the defect is measured and a mesh size appropriately chosen for a minimum of a 3- to 5-cm overlap.

There has been some debate about the necessity of transfascial sutures. The controversy stems from the pain caused by these sutures. However, they facilitate centering the mesh about the hernia defect and add to the stability of the mesh. Transfascial sutures have been associated with decreased recurrence rates compared to tacker fixation alone.\textsuperscript{16} However, a meta-analysis comparing suture fixation to tacker fixation alone demonstrated decreased operative times and postoperative pain with the tacker, with no difference in recurrence rates.\textsuperscript{17} It is the authors’ preference to use transfascial sutures placed every 4 to 6 cm. The sutures are placed extracorporeally and mapped to the abdominal wall to ensure the mesh
overlap is a minimum of 3 cm in all directions. Tacks are then used to secure the edges of the mesh circumferentially.

Occasionally, drains are placed in large defects to prevent seroma formation, but they are typically not needed for LIHR. Patients can be discharged home the same day but are often kept overnight for adequate pain control. The use of an abdominal binder is recommended with larger defects to stabilize the abdominal wall and decrease the risk of seroma formation.

**SHORT-TERM FOLLOW-UP**

A multicenter Veterans Administration randomized controlled trial comparing laparoscopic ventral incisional hernia repair to open mesh repair demonstrated lower complication rates in the laparoscopic group with an earlier time to resume work activities. However, the time to resume daily activities was similar in both groups. Other studies have demonstrated no difference in postoperative pain or recovery at 3 weeks, and patients who underwent an LIHR reported better physical function. Overall, laparoscopic repair has been associated with lower 30-day morbidity than open repair.

**LONG-TERM FOLLOW-UP**

Recurrence rates of 2.7% and 15.5% at follow-up greater than 20 months have been reported for LIHR. Five-year recurrence rates are reported at 29%. Risk factors for recurrence include large defects, obesity, previous open repairs, and perioperative complications.

**CONCLUSION**

There are no data to establish that laparoscopic incisional hernia repair is superior to open incisional hernia repair for use in all incisional hernias. When selecting LIHR, many factors should be taken into consideration such as hernia size, location, recurrence, and comorbid conditions. It is imperative that surgeons understand when LIHR is likely to be beneficial compared with open repair. Careful selection of appropriate patients, vigilance during the enterolysis, and proper surgical technique can ensure a successful hernia repair.
REPRESENTATION

REFERENCES


INTESTINAL STOMAS

Cindy Kin • Mark Lane Welton

INTRODUCTION

Permanent or temporary fecal diversion is necessary for the surgical management of a wide variety of colorectal conditions including bowel obstruction, low pelvic anastomoses, poor sphincter function, difficult bowel regimen in spinal cord injury, rectal cancers and other pelvic malignancies, inflammatory bowel disease, perineal soft tissue infection, decubitus ulcers, and traumatic perineal injury.

Intestinal stomas carry significant social implications, and the prospect of having one commonly engenders very strong reactions from patients and their families. Many are initially filled with a sense of dread over “the bag.” However, for many patients, having an intestinal stoma can dramatically improve quality of life and allow them to regain control over their lives. For example, those with poor bowel function causing frequency, urgency, or incontinence may find themselves spending hours each day in the bathroom, fearful of leaving the house, and anxious when they are not near a bathroom. An intestinal stoma can allow them to reintegrate into normal life. While a well-functioning and well-placed stoma is compatible with an excellent quality of life, a poorly constructed stoma that cannot be reliably pouches can
wreak havoc on a patient’s life.

The goal of this chapter is to serve as a resource for surgeons who create and close stomas, so that their patients can have the best possible functional outcome. The chapter discusses preoperative planning and decision-making, technical details of how to create intestinal stomas, and management of stoma complications.

The main technical principles for optimal stoma construction include proper stoma siting on the abdominal wall, adequate mobilization of the bowel, preservation of blood supply, and eversion of the bowel wall during stoma maturation. The important nontechnical considerations include providing education and support for patients with stomas, and knowing how to manage stoma-related complications.

Stoma construction requires attention not only to the bowel anatomy but also the abdominal wall anatomy. The most ideal segment of colon to use for a colostomy is the descending colon or proximal sigmoid colon, as using the distal end of a floppy sigmoid colon increases the risk of prolapse. For ileostomy creation, the most distal segment of small bowel that will reach through the abdominal wall should be used. Often it is necessary to ligate mesenteric vessels for oncologic or mobilization purposes. Ensuring that the marginal artery is intact for colostomies and that the arcade of ileal vessels is intact for ileostomies is critical for preventing stoma ischemia. The length and thickness of the mesentery affect whether the stoma will reach through the abdominal wall adequately to create a stoma that is not under tension. A short, thick mesentery may require more extensive mobilization to create a good stoma. Abdominal wall thickness and contour are important considerations during stoma creation. Thick abdominal walls require more mobilization of the bowel so that the stoma will reach through the abdominal wall without tension. Creases and scars on the abdominal wall surface play a major role in choosing the optimal site for the stoma.

PREOPERATIVE CONSIDERATIONS

Enterostomal Therapists

The surgeon’s greatest ally in the work of taking care of patients with intestinal stomas is the enterostomal therapist (ET), a nurse specializing in the
care of stomas. Patients undergoing elective operations in which a permanent or temporary stoma is planned should undergo preoperative counseling by both their surgeon and an ET. Dedicated care by a specialized ET is associated with better quality of life for patients with new stomas, measured by less self-consciousness and fearfulness, improved facility with stoma care, less pain, and better sleep.\(^1\) Emotional or social support services may be necessary for ostomates in the preoperative or postoperative period, as many patients, especially women, struggle with coping and adjustment issues, poor body image, depression, and challenges with sexuality and intimacy.\(^2\) In addition to providing prospective ostomates with support and education, ETs are also trained to mark appropriate stoma sites.

### Stoma Site Marking

Patients who undergo preoperative marking for stomas are more likely to be able to independently care for their stomas, have more predictable pouching with regard to length of time and leaks, and resume normal life after surgery.\(^3\) Surgeons who perform these operations must also be skilled in choosing optimal ostomy sites, as a preoperative ET session is not always feasible due to timing of operative intervention and scarce resources. The optimal site for an intestinal stoma is within the rectus abdominis muscle, free of creases, and visible to the patient. The most commonly chosen stoma site is in the outer third of the rectus muscle, at the summit of the infraumbilical fat pad. Ileostomy sites are usually in the right lower quadrant, and colostomy sites are usually in the left lower quadrant (Figs. 15-1 and 15-2). However, obesity, prior scars, or other patient-related factors will often necessitate stoma placement in other locations (Fig. 15-3). Additional considerations are noted in Table 15-1. Except in cases involving the sickest of patients, surgeons should be able to mark at least one optimal site before emergent operations. If the patient is able to sit up, then the surgeon can ensure the absence of creases through the planned site and that the patient will be able to see and manage the stoma. A more detailed procedure for marking the stoma site in the elective setting is described in Table 15-2. Preoperative stoma site marking is associated with a lower risk of postoperative complications, improved postoperative quality of life, and higher levels of independence in care.\(^4,5\)
FIGURE 15-1 Placement of ileostomy in the right lower quadrant, within the rectus muscle and at the apex of the infraumbilical fat mound.
**FIGURE 15-2** Placement of colostomy in the left lower quadrant, within the rectus muscle and at the apex of the infraumbilical fat mound.

**FIGURE 15-3** Creases, scars, and obesity affect the optimal placement of stomas.

**TABLE 15-1: KEY CONSIDERATIONS FOR CHOOSING AN OPTIMAL STOMA SITE**

1. The stoma should be located in the outer third of the rectus abdominus muscle.
2. Physical characteristics of the torso: a protuberant abdomen or large pannus, abdominal folds, scars, location of the costal margin and iliac crest, pendulous breasts, and hernias.
3. Patient characteristics: mobility (wheelchair-bound), posture (kyphosis), dexterity, vision.
4. Patient preference for location, based on belt line and other individual factors.
5. Surgical considerations: type of stoma (loop vs end), segment of intestine to be used for the stoma, continent vs incontinent, need for both fecal and urinary stomas.
TABLE 15-2: PROCEDURE FOR MARKING THE STOMA SITE
1. Explain the purpose of preoperative stoma marking to the patient, and invite the patient to participate in the process.

2. Examine the surface of the abdomen in various positions. Take note of folds, creases, scars, and contour. Take note of waistbands and any other accessories on the torso such as braces or other ostomy pouches.
   - When the patient is fully clothed in a seated position, note the position of the waistband and any associated abdominal folds.
   - If the patient uses a wheelchair or other assistive devices, examine them in their normal position and posture.
   - All clothing covering the abdomen (shirt and pants) should be completely removed.
   - Examine the abdomen while the patient is standing up, lying down, sitting, and bending forward. Note any changes in folds, creases, and contour.

3. Identify the lateral edge of the rectus abdominis muscle by having the patient lie down and raise the head to look down at the feet.

4. Mark one or more spots on the skin within the rectus abdominis muscle, at least 2 inches away from the midline, on a flat surface, away from scars or creases, and on the appropriate side for the planned operation. The highest priority is a flat surface for pouching.

5. Have the patient lie down, sit up, bend forward, and stand up, checking to make sure the area around the mark(s) remains a flat pouching surface, free of creases, in all positions.

6. Make sure the patient can see the mark(s) when they are lying down, sitting up, and standing up.

7. Stoma placement in the upper abdominal quadrants may be more easily seen and accessed for the patient with a large, protuberant abdomen.

8. If there is more than one option for stoma placement, number them in order of patient preference. Take into account where the waistband normally sits, and try to avoid that as a stoma site.
Bowel Preparation

Mechanical bowel preparation and nonabsorbable oral antibiotics are recommended prior to elective colorectal operations, as they are associated with lower rates of surgical site infections, anastomotic leak, ileus, and readmission.\textsuperscript{6–8} The original Nichols and Condon oral antibiotic regimen from the 1970s of neomycin and erythromycin base can still be used, or metronidazole can be used in place of erythromycin base.\textsuperscript{9} Table 15-3 describes the options for mechanical bowel prep and oral antibiotic regimens. Mechanical bowel prep in the absence of oral antibiotics is not recommended. Mechanical bowel prep and oral antibiotics may not be necessary in all types of colorectal operations; this regimen was not shown to decrease complications in patients undergoing total colectomy,\textsuperscript{7} and should not be used in patients with ileostomies.

\begin{table}[h]
\centering
\caption{Preoperative Mechanical Bowel Prep and Oral Antibiotic Regimens}
\begin{tabular}{|c|c|}
\hline
Regimen & Description \\
\hline
Neomycin & \textit{Short-acting preoperative bowel prep with neomycin} \\
\hline
Erythromycin & \textit{Short-acting preoperative bowel prep with erythromycin} \\
\hline
Metronidazole & \textit{Short-acting preoperative bowel prep with metronidazole} \\
\hline
\end{tabular}
\end{table}
Commonly Used Mechanical Bowel Preparations
Polyethylene glycol 3350 and electrolytes (GoLYTELY® and Colyte®): 8 oz. every 10 minutes until 4L consumed or rectal effluent clear.
Polyethylene glycol 3350, sodium chloride, sodium bicarbonate, potassium chloride (NuLYTELY®): 8 oz. every 10 minutes until 4L consumed or rectal effluent clear.
Polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid (MoviPrep®): 8 oz. every 15 minutes until 1L consumed.
Suprep® (sodium sulfate, potassium sulfate, magnesium sulfate): 6 oz. the evening before, 6 oz. the morning of procedure.
Magnesium citrate: 10 oz. magnesium citrate with 8 oz. water every hour for 4 hours; repeat regimen 4 hours later.

Oral Antibiotic Regimens
Neomycin 1 gram orally at 2 pm, 3 pm, and 10 pm
PLUS
Erythromycin base 1 gram orally at 2 pm, 3 pm, and 10 pm
OR
Metronidazole 500 mg orally at 2 pm, 3 pm, and 10 pm

COLOSTOMY

End Colostomy

INDICATIONS
The most common operations that involve the creation of an end colostomy are abdominoperineal resection of the rectum and Hartmann’s procedure, in which proctectomy and/or sigmoidectomy is performed without colorectal anastomosis. Patients who undergo reoperation for takedown of a leaking colorectal anastomosis also require creation of an end colostomy. Another indication for end colostomy is the need for complete temporary or permanent fecal diversion for nonobstructive pathology such as a rectourethral or rectovaginal fistula, necrotizing soft tissue infection of the
perineum, or severe trauma to the rectum, anus, or perineum. A devastating consequence of landmines is severe lower extremity, pelvic, and perineal trauma sustained by both military personnel and civilians in conflict zones. Extensive perineal trauma requires early fecal diversion with end colostomy to completely prevent stool from contaminating the perineal wound. In such cases, the benefit of complete fecal diversion outweighs the slightly greater difficulty in closing end colostomies than closing loop colostomies. If takedown of an end colostomy is planned, consider covering the distal staple line and wrapping the colostomy in an adhesion barrier such as Seprafilm® to decrease adhesions to both structures. These measures may facilitate subsequent laparoscopic and open procedures. Another option for cases of extensive perineal injury is the divided loop colostomy, which we discuss in a subsequent section. An end colostomy is not an acceptable solution for a distal obstruction, as stapling off the distal side of the colon will create a closed loop between the staple line and the obstruction, which may eventually result in perforation at the staple line.

**OPEN TECHNIQUE**

Place Kocher clamps on the dermis and on the fascia of the abdominal wall, on the side of the planned stoma, to stabilize the layers of the abdominal wall in relation to each other. With another hand in the abdomen, hold a folded laparotomy sponge firmly up against the anterior abdominal wall at the planned stoma site, to ensure that no inadvertent bowel injury occurs during the creation of the stoma defect. Excise a disk of skin at the previously marked stoma site. Some surgeons prefer to core out the subcutaneous fat, while others prefer to incise the fat and spread it apart using Army-Navy or lateral retractors to expose the fascia. Once the fascia is exposed, make a vertical or cruciate incision to expose the underlying rectus muscle. Place a curved Mayo clamp through the rectus muscle, and open the clamp to spread the muscle fibers medially and laterally, exposing the posterior rectus sheath. Make a vertical or cruciate incision in the posterior sheath, exposing the laparotomy sponge that is being pushed against the inside of the anterior abdominal wall (Fig. 15-4).
Pass the Mayo or large Peon clamp, depending on body habitus, through the defect and bring the end of the clamp through the midline incision. Use the clamp to hold up the abdominal wall to expose the stoma defect from the inside, to facilitate a check for hemostasis, as there may be some hemorrhage from the muscle fibers or inferior epigastric branches. Dilate the defect to two to three fingerbreadths, depending on the size of the surgeon’s fingers and the caliber of the bowel.

Ensure that the colon is oriented correctly and that there is adequate mobilization of the colon to bring it through the abdominal wall without tension. If proctectomy with ligation of the inferior mesenteric artery is being performed, then the left colon will need to be mobilized adequately and used for the stoma, as the sigmoid colon blood supply may be compromised in this case (Fig. 15-5). Insert a Babcock clamp through the stoma defect to grasp the end of the colon. Gently bring the colon through the defect by guiding it with the Babcock while pushing it from the inside of the abdomen (Fig. 15-6). Excess traction with the Babcock will result in a tissue trauma. Ensure that at least a few centimeters of colon sit without tension above the skin, and that it is well-perfused. Insert a finger alongside the colon through the stoma defect to ensure that the defect is not too tight.
FIGURE 15-5 Be sure to mobilize the left colon for the colostomy if high ligation of the inferior mesenteric artery was performed, to avoid stoma ischemia.
FIGURE 15-6 Bring the end of the colon and its mesentery through the stoma defect, ensuring that there is adequate length so that there is no tension. This will prevent stoma retraction.

Some surgeons suture the free edge of the colon mesentery to the lateral abdominal wall, but this technique has not been shown to reduce the risk of bowel obstruction, hernia, or prolapse (Fig. 15-7). After abdominal closure, remove the staple line from the end of the colon and place absorbable sutures of 3-0 Chromic or 3-0 Vicryl in all four quadrants through the full thickness of the colon wall and to the dermis or epidermis. Then place additional sutures between those four stay sutures (Fig. 15-8). Some surgeons will create a colostomy that is slightly budded so that it protrudes slightly from the level of the skin, while others prefer a skin-level colostomy. For obese patients in whom the risk of retraction is higher, and for patients with underlying gastrointestinal disorders that may lead to liquid stool output, budded stomas are preferable to skin-level stomas for improved pouching.
FIGURE 15-7 Suturing the free edge of the colon mesentery to the lateral abdominal wall may close the lateral space, but it has not been shown to reduce the risk of bowel obstruction, hernia, or prolapse.
Prophylactic mesh placement at the time of primary stoma creation may prevent parastomal hernia. The use of a retromuscular polypropylene mesh to reinforce the abdominal wall around the stoma was not associated with higher rates of infection or stricture in the multicenter randomized controlled PREVENT trial. Multiple randomized controlled studies have examined the risk of parastomal hernia with or without prophylactic mesh placement. While results vary across studies, it does appear that there is likely to be an advantage for parastomal hernia prevention in patients who undergo prophylactic mesh placement. Long-term results of the ongoing PREVENT trial are pending.

The two methods for placing prophylactic mesh around a colostomy are the Sugarbaker and keyhole techniques. The modified Sugarbaker technique uses an intraperitoneal onlay mesh covering the stoma defect and the most distal segment of the colon before it exits the abdominal wall via the stoma defect. The mesh maintains the colon in a lateral position and acts as a tunnel through which the distal colon travels before exiting through the abdominal wall as the stoma. The mesh is affixed with transfascial sutures.
The keyhole technique uses mesh with a hole or cruciate defect corresponding to the stoma defect, allowing the colon to pass through the mesh. The mesh can be placed against the peritoneal surface of the anterior abdominal wall or in the retromuscular space.\textsuperscript{15}

Another technique to reduce the risk of stoma prolapse or parastomal hernia is the creation of an extraperitoneal tunnel from the stoma defect to the lateral abdominal wall. The opening in the peritoneum is lateral to the rectus muscle and the colon runs through a tunnel between the peritoneum and rectus muscle before exiting through the stoma defect. Several studies have shown that the extraperitoneal route compared to transrectus placement reduces the risk of stoma prolapse and parastomal hernia.\textsuperscript{21–23}

To create the extraperitoneal tunnel, make the stoma defect as usual in the skin and fascia and spread the rectus muscle to expose the posterior rectus sheath. Instead of incising this layer, continue the dissection laterally within this plane, separating the rectus muscle away from the peritoneum. Make a vertical incision in the peritoneum at the lateral end of the extraperitoneal tunnel. The peritoneal incision must be large enough to accommodate the colon and not cause an obstruction. Bring the colon through the extraperitoneal tunnel and up through the stoma defect. Check to make sure that there is enough space within the tunnel so that a finger can be inserted alongside the colon within the tunnel, and make sure that the tunnel does not cause kinking of the colon that may cause an obstruction.

Placement of prophylactic mesh and creation of an extraperitoneal tunnel may be helpful in reducing parastomal hernia risk for patients with permanent colostomies, but should be avoided for those with temporary colostomies as the colostomy reversal process will be much more difficult.

**LAPAROSCOPIC TECHNIQUE**

The stoma defect can be made during pneumoperitoneum by excising a disk of skin and subcutaneous tissue at the previously marked site, dividing the fascia, spreading the muscle, and incising the peritoneum. Use two fingers to dilate the stoma defect and maintain pneumoperitoneum. After making the stoma defect, bring the end of the colon through the defect while ensuring proper orientation with laparoscopic vision. Slide a Babcock clamp through the stoma defect alongside the fingers to grasp the colon under laparoscopic vision, and then bring the end of the colon through the defect. If the end of
the colon reaches through the stoma defect while the abdomen is insufflated, then the colon is adequately mobilized. It is important to remember that pneumoperitoneum stretches the abdominal wall, and may thus make the stoma defect larger under insufflation than it will be after desufflation. Thus, confirm that the stoma defect is adequately sized by ensuring that an index finger can be passed through the defect alongside the stoma after desufflation.

Prophylactic mesh reinforcement of the stoma defect using the modified Sugarbaker or keyhole technique is amenable to a laparoscopic or robotic approach. Fixation of the mesh with both tacks and transfascial sutures mirrors the standard technique of minimally invasive ventral hernia repair. Ensure that the tacks and sutures do not violate the bowel, and that the tunnel is wide enough to accommodate the colon.

Creation of an extraperitoneal tunnel is also amenable to a minimally invasive approach. Create the stoma defect through the skin, fascia, and muscle, but not through the peritoneum. Laparoscopically Incise the peritoneum lateral to the stoma defect to form the proximal opening of the tunnel. Create the extraperitoneal tunnel by passing a curved Mayo clamp between the rectus muscle and posterior rectus sheath. Dilate that tract so that it is broad enough to accommodate the colon without causing an obstruction. Then, bowel graspers can be used to bring the end of the colon into the proximal opening of the tunnel, and a Babcock clamp can be passed through the tunnel from the stoma defect to bring it through the tunnel and out the defect.

**TECHNIQUE FOR TAKEDOWN OF AN END COLOSTOMY**

Preoperative contrast enema or flexible sigmoidoscopy prior to colostomy closure is critical for assessing the rectal stump for length, leaks, and strictures. Colonoscopy of the proximal colon may be necessary if not done recently. Mobilize the colostomy by making a circumferential incision in the peristomal skin, leaving a 3-mm rim of skin on the bowel to aid in retraction. Place Allis clamps on the skin rim for retraction and sharply dissect the bowel free from the surrounding soft tissue and fascial defect. Staple the end of the colon closed and re-prep the abdomen. Drop the colon into the abdomen if full mobilization from the abdominal wall was possible.
Open or laparoscopic approaches are options for the remainder of the operation, depending on the surgeon’s expertise and the density of intra-abdominal adhesions. For laparoscopic cases, place a “glove port” through the stoma site to allow for insufflation. Place a small ringed wound protector through the stoma site. Place the wrist of a size 6 glove over the outer ring and roll the wrist of the glove down with the outer ring, creating an air-tight seal. Place up to three ports of any size through the fingers of the glove by cutting off the fingertips, and tying the ports in place with 0-silk ties. Place additional ports through the abdominal wall as needed. Mobilize the small bowel out of the pelvis to expose the rectal stump. Identify the top of the rectal stump and its staple line. Ensure that neighboring structures, including the vagina, seminal vesicles, bladder, and ureters, are out of the way.

Mobilize the colon proximal to the stoma in order to create a tension-free colorectal anastomosis. Once this is accomplished, a side-to-end or end-to-end anastomosis can be created, using the circular EEA stapler. If the anastomosis is low or otherwise high risk, and a proximal diverting loop ileostomy is indicated, then consider bringing the loop ileostomy through the existing stoma defect.

If diversion is not necessary, close the fascial defect with interrupted 0-Vicryl sutures. Cinch the skin defect with a 2-0 Vicryl purse-string placed in the dermal layer. This closure allows for drainage and healing by secondary intention in order to prevent wound infection, while minimizing the size of the scar.

**Loop Colostomy**

**INDICATIONS**

The primary indication for loop colostomy is a distal obstruction requiring temporary or palliative fecal diversion. Patients with symptomatic fistulas between the rectum and urethra, bladder, or vagina may also find relief with a loop colostomy. A downside of using the colon rather than the ileum for diversion in the case of fistula is the potential compromise of a segment of colon that may be needed to reach a low pelvic anastomosis for the purposes of reconstruction. Other indications for loop colostomy include trauma to the extraperitoneal rectum or perineum, and complicated soft tissue infection of the perineum requiring significant debridement. A loop colostomy may
divert a high-risk distal anastomosis, but a loop ileostomy is the more common choice. As a loop colostomy may be incompletely diverting if the posterior wall sits below skin level, ongoing distal fecal drainage may require conversion to an end colostomy.

The ideal segment of colon to use for a loop colostomy is the sigmoid, as it is the most mobile part of the distal colon. In cases of unresectable obstructing lesions at the splenic flexure or left colon, or when the sigmoid is not available for use, the use of the transverse colon may be necessary. Loop transverse colostomies are associated with a high rate of complications including prolapse and pouching difficulties due to liquid output, and should be avoided unless absolutely necessary. Strong consideration should be given to a diverting loop ileostomy rather than a diverting transverse colostomy, as loop ileostomies are associated with lower complication rates and do not compromise subsequent definitive colorectal procedures.

**OPEN TECHNIQUE**

Make the stoma defect in the fashion described for end colostomy. Mobilize the loop of sigmoid or transverse colon so that it will reach through the abdominal wall. Make a defect at the junction between the colon and the mesentery, and pass a ½-inch umbilical tape or Penrose drain through this defect. Prior to bringing the bowel through the abdominal wall, wrap the bowel in Seprafilm to facilitate the takedown procedure. Use an umbilical tape or Penrose drain to guide the loop of colon through the stoma defect while pushing it out from the inside of the abdomen (Fig. 15-9). Excess traction on the umbilical tape or Penrose drain may cause tearing of the bowel or mesentery. After closing the abdominal incision, mature the loop colostomy. Some surgeons prefer the use of stoma rods that can be placed through the mesentery defect to replace the umbilical tape. Transversely incise the antimesenteric border of the distal side of the loop. This division should be more than half the bowel circumference so that the functioning proximal limb and nonfunctioning distal limb are separated. Suture the free edge of the bowel to the dermis or epidermis with interrupted 3-0 Chromic sutures. Eversion of the proximal limb, and making sure the posterior wall is at least at the level of the fascia, will prevent stool from passing into the distal limb.
FIGURE 15-9 Use an umbilical tape to guide the loop of colon through the stoma defect while pushing it out from the inside of the abdomen. Excess traction on the umbilical tape may cause tearing of the bowel or mesentery.

LAPAROSCOPIC TECHNIQUE

If a laparoscopic approach is safe and feasible, mobilize the loop of colon adequately to reach the anterior abdominal wall while the abdomen is insufflated. Make the stoma defect and dilate it to two to three fingerbreadths under pneumoperitoneum, and slide a Babcock clamp alongside the fingers to grasp the mobilized loop of colon. Bring the loop gently through the stoma defect. Check laparoscopically to determine the orientation of the colon, and mature the proximal side.

A single-port or reduced-port laparoscopic technique using the planned stoma site as the port site results in fewer or no additional incisions aside from the stoma defect itself. The additional cost of a single-port access system can be avoided by using a glove port as described in the previous section.

TECHNIQUE FOR CLOSURE OF LOOP COLOSTOMY

Loop colostomy closure starts with a circumferential incision around the
colostomy, about 3 mm from the mucocutaneous junction. Use this skin edge for retraction by placing Allis clamps on it while sharply dissecting the bowel wall away from the subcutaneous tissue and fascia. In the rare event that this dissection is so difficult that mobilization of the colon from the abdominal wall is not possible through the stoma site, a midline incision may be necessary. When the colon is completely mobilized from the abdominal wall, unevent the proximal and distal bowel edges (Fig. 15-10). Examine the bowel wall for partial- or full-thickness defects and repair them transversely with interrupted 3-0 Vicryl sutures. If the colon is largely intact, then resection is not necessary. Trim away the skin edge, leaving only a transverse defect in the antimesenteric aspect of the colon (Fig. 15-11). Close the defect transversely using interrupted 3-0 absorbable seromuscular sutures (Fig. 15-12). To handle a significant size discrepancy between the proximal and distal limb, make a longitudinal slit in the antimesenteric side of the smaller limb (Cheatle slit). Match the apex of the Cheatle slit to the midpoint of the larger caliber bowel edge. Close the defect transversely. A stapled closure using a linear noncutting stapler to close the bowel transversely is another option (Figs. 15-13 and 15-14). A final option is to create a side-to-side stapled anastomosis by firing a linear cutting stapler down the lumens of the proximal and distal limbs and closing the end of the anastomosis with a linear stapler.

**FIGURE 15-10** To take down a loop colostomy, completely mobilize the bowel from the surrounding subcutaneous tissue and fascia.
**FIGURE 15-11** Trim away the skin edge, leaving only a transverse defect in the antimesenteric aspect of the colon.

**FIGURE 15-12** Close the defect transversely with interrupted seromuscular sutures using 3-0 absorbable sutures.
FIGURE 15-13  A linear stapler can also be used to close the defect.

FIGURE 15-14  A linear stapler can also be used to close the defect.

If resection of a colon segment is necessary due to injuries sustained during mobilization of the colostomy, then create the anastomosis in a handsewn end-to-end fashion, or a stapled side-to-side fashion. Closure of the fascial defect and skin is described in the previous section.
Blowhole Colostomy

The original blowhole colostomy described by Turnbull was for the indication of toxic megacolon due to severe ulcerative colitis. Combined with loop ileostomy, blowhole colostomy is a minimally invasive way to decompress the colon and allow these very sick patients to recover until they are stable enough to undergo colectomy. With modern management of ulcerative colitis, we rarely encounter this clinical situation, but a blowhole colostomy may be a lifesaving intervention in the very critically ill patient with toxic colitis or obstruction who is too unstable to undergo resection or a formal colostomy.

The blowhole colostomy is a minimally invasive way to decompress the colon. First, localize the transverse colon by taping a coin on the patient’s epigastrium and taking an abdominal film. Determine the location of the transverse colon by using the location of the coin in relation to the most dilated part of transverse colon as a guide. With local anesthetic, make an incision in the mid-epigastrium right over the transverse colon. Incise the fascia and peritoneum to expose the serosa of the transverse colon. Place interrupted sutures of 3-0 Vicryl between the seromuscular layer of the bowel and the peritoneum to secure the colon to the abdominal wall and to isolate this window of bowel from the rest of the abdominal cavity. The colon will be very thin walled and prone to tearing, and is likely to leak gas or stool through the needle holes. Then, decompress the gas in the dilated colon using a large-bore needle (Fig. 15-15). Place another layer of interrupted 3-0 Vicryl sutures between the seromuscular layer of the bowel and the fascia. Incise the colon and suction out the gas and stool that is under pressure (Figs. 15-16 through 15-18). Place interrupted sutures between the full thickness of the bowel wall edge to the skin (Figs. 15-19 through 15-21).
FIGURE 15-15 Place interrupted sutures between the peritoneum and the bowel to quarantine the bowel. Decompress the gas out of the colon using a large-bore needle.

FIGURE 15-16 After placing another layer of interrupted sutures between the fascia and the bowel, incise the bowel wall and suction out more colonic
FIGURE 15-17 After placing another layer of interrupted sutures between the fascia and the bowel, incise the bowel wall and suction out more colonic contents.

FIGURE 15-18 After placing another layer of interrupted sutures between the fascia and the bowel, incise the bowel wall and suction out more colonic contents.
FIGURE 15-19 Place interrupted sutures between the full thickness of the bowel wall edge and the skin edge.

FIGURE 15-20 Place interrupted sutures between the full thickness of the bowel wall edge and the skin edge.
FIGURE 15-21  The blowhole colostomy is located usually in the midline epigastric position.

**Divided Loop Colostomy (Separated Loop Colostomy)**

**INDICATIONS**

The indications for a divided loop colostomy are similar to those for a loop colostomy, which include a distal obstruction, a symptomatic fistula between the rectum and urethra, bladder, or vagina, trauma to the extraperitoneal rectum or perineum, and complicated soft tissue infection of the perineum with a large perineal wound.\(^{10-12}\) The benefit of a divided loop colostomy over a loop colostomy is more definitive fecal diversion. A divided loop colostomy has two advantages over an end colostomy: reversal of a divided loop colostomy can be performed through the stoma site, and it can be used in the case of distal obstruction since the distal limb remains open.
TECHNIQUE

Mobilize the loop of colon, create the stoma defect, and bring the loop of colon through the defect in the same fashion as a loop colostomy. Make a defect in the mesentery adjacent to the bowel wall, avoiding the mesenteric vasculature. Divide the colon with a linear cutting stapler. Excise the corner of the distal staple line and suture the bowel wall to one side of the stoma defect, creating a mucus fistula. Remove the entire staple line of the proximal limb, and mature the colostomy with interrupted full-thickness 3-0 Chromic sutures to the skin. Part of the colostomy will be adjacent to the mucus fistula. Suture the bowel wall edges together.

Converting a loop colostomy to a divided loop colostomy is indicated if there is persistent and symptomatic drainage of feces distally, which occurs because the posterior wall of the loop colostomy has fallen below the level of the fascia. Incise the stoma circumferentially at the mucocutaneous junction. Sharply dissect the bowel free of the surrounding subcutaneous tissue and fascia to bring the entire width of the colon above the skin level. Create a defect in the mesentery adjacent to the bowel and divide it with a linear cutting stapler. Mature the colostomy and the mucus fistula.

**Loop-End Colostomy**

**INDICATIONS**

A patient with a short colonic mesentery and/or thick abdominal wall that precludes the end of the colon to reach through the abdominal wall may require a loop-end colostomy. The segment just proximal to the distal end of the colon will often reach farther through the abdominal wall than the end.

**TECHNIQUE**

Mobilize the colon and create a stoma defect. Make a defect at the bowel-mesentery border and pass a ½-inch umbilical tape or Penrose drain through the defect. Use this to guide the loop of colon through the defect while pushing the colon and mesentery from the inside. Wrap the bowel in Seprafilm prior to passing through the abdominal wall if the stoma is temporary. Exchange the umbilical tape for a stoma rod and suture it in place. Divide the colon transversely at the distal side of the loop. Mature the stoma.
as a loop colostomy.

**Colostomy Function**

Colostomy function varies greatly among patients and depends on several factors, including diet and fluid intake, and preexisting bowel habits. While most patients wear stoma appliances at all times, a smaller proportion of patients choose to irrigate their colostomies to reduce the need to wear an appliance. Colostomy irrigation is a daily high-volume enema and gives patients control over the timing of bowel movements. Patients who irrigate successfully may only need to wear a bandage or a gauze pad over the colostomy for the rest of the day. Patients who use colostomy irrigation have decreased flatus and odors, and higher quality of life compared to those who do not use irrigation. Water or agents such as polyethylene glycol or glycercyl trinitrate solution are the irrigants most commonly used.\(^{27,28}\)

**ILEOSTOMY**

The consistency of ileostomy output is more watery, and the composition is more caustic to the skin. These two differences increase the risk for pouch leaks and subsequent skin breakdown in patients with ileostomies compared to those with colostomies. It is very important that ileostomies be budded to allow the os to be above the surface of the skin and within the pouch, decreasing the risk of pouch leakage.

**End Ileostomy**

**INDICATIONS**

Patients undergoing total colectomy or total proctocolectomy without restoration of intestinal continuity require end ileostomy. Disease processes include ulcerative colitis, Crohn’s colitis, familial adenomatous polyposis, ileocolic anastomotic leak requiring reoperation and takedown of the anastomosis, and colonic inertia without ileorectal anastomosis.

**TECHNIQUE**
Mobilize the ileal mesentery off the retroperitoneum up to the duodenum so that the end of the ileum will reach through the anterior abdominal wall (Fig. 15-22). Ensure that there is adequate blood supply to the ileum by preserving the arcade of mesenteric vessels adjacent to the end of the ileum (Fig. 15-23). Make the stoma defect as described for a colostomy, but only dilate to two fingerbreadths (Fig. 15-24). If the end ileostomy is temporary, wrap the stoma in Seprafilm to facilitate subsequent takedown, and then gently guide the ileum through the defect (Fig. 15-25). After closing the abdominal wall, mature the ileostomy by removing the staple line and placing four sutures of 3-0 Chromic full-thickness through the free edge of the ileum, through the seromuscular layer at the base of the stoma, and the dermis. Holding these sutures out, use the back of a small forceps inserted under the free edge to gently create a budded configuration by everting the bowel. Tie down these sutures and place additional sutures full thickness through the free edge of bowel and to the dermis (Figs 15-26 and 15-27).
Mobilize the ileal mesentery off the retroperitoneum so that the end of the ileum will reach through the anterior abdominal wall without tension.
FIGURE 15-23  Preserve the arcade of mesenteric vessels adjacent to the end of the ileum.
FIGURE 15-24 The Kocher clamps will keep the fascial layers in line. The anterior rectus sheath is incised, the muscle is spread, and the peritoneum is incised to make the stoma defect.
**FIGURE 15-25** Bring the ileum with its blood supply through the stoma defect.

**FIGURE 15-26** Remove the staple line from the end of the ileum.
Evert the end of the ileum with interrupted 3-0 Chromic sutures, through the full thickness of the bowel wall edge to the dermis of the skin.

**TECHNIQUE FOR END ILEOSTOMY TAKEDOWN**

The technique for taking down an end ileostomy involves mobilizing the ileostomy from the skin, subcutaneous tissue, and fascia as one would do for a colostomy. Use sharp dissection to turn the everted end of the bowel inside. Check for any full- or partial-thickness defects in the bowel wall. Close the end of the ileum by stapling it with a linear cutting stapler. Re-prep the abdomen and change to sterile gloves and instruments before making the abdominal incisions needed for the anastomosis. To maintain pneumoperitoneum at the stoma site with the laparoscopic approach, either close the stoma site fascia with interrupted 0-Vicryl before insufflation or use the stoma site as a port site.

**Loop Ileostomy**

**INDICATIONS**

The indications for a loop ileostomy include a distal colonic obstruction in the setting of an incompetent ileocecal valve, a distal colorectal anastomosis with a high risk for an anastomotic leak, severe perianal Crohn’s disease,
perineal or perianal trauma, perineal wounds that require fecal diversion, and fistulas between the bowel and genitourinary tract which are not ready for definitive repair.

**TECHNIQUE**

Choose as distal a segment of ileum as possible that will reach without tension through the abdominal wall. Place orienting sutures of loosely tied knots to prevent inadvertent maturation of the distal side (Fig. 15-28). Make a small defect in the mesentery just adjacent to the bowel wall, taking care not to damage the mesenteric vasculature. Bring a ½-inch umbilical tape or Penrose drain through this defect.

**FIGURE 15-28** Select the most distal segment of ileum that will reach
without tension through the abdominal wall, and place orienting proximal and distal sutures on the bowel wall.

The ileostomy defect is created in the same manner as for an end ileostomy. The chosen loop of ileum is wrapped in Seprafilm and brought through the ileostomy defect using the tape to guide the loop through the abdominal wall while pushing the loop of bowel through the defect from the inside out. Placing excess traction on the bowel and mesentery can cause the mesentery or bowel wall to tear. The mesentery–bowel junction should be at the level of the skin.

After fascial closure and before stoma maturation, some surgeons prefer to place a stoma rod through the mesenteric defect to prevent ileostomy retraction. In obese patients it is critical to sew the rod or Robnel to the skin, as it might otherwise fall into the abdominal cavity, necessitating reoperation. Remove the stoma rod 3 to 5 days after the operation.

Mature the loop ileostomy by transversely incising the distal side of the loop. This transverse enterotomy should encompass at least half the circumference of the bowel wall. Place three-point sutures of 3-0 Chromic full-thickness through the free edge of the bowel, seromuscular through the bowel at the base of the stoma, and through the dermis. Place these sutures in the midline of the antimesenteric bowel wall and on each side near the stoma rod. While placing gentle tension on the sutures, evert the stoma by pushing the back of a forceps just under the free edge of the bowel. Tie the sutures down. Suture the distal bowel with interrupted 3-0 Chromic sutures between the full-thickness bowel wall and dermis. Place additional sutures between these initial sutures to fill in the gaps (Fig. 15-29).
FIGURE 15-29 Use three-point sutures to evert the proximal limb of the loop ileostomy (inferior limb in this figure) so that the functional lumen is budded. The distal lumen (superior limb in this figure) can be at the skin level.

COMPLICATIONS

Patients with loop ileostomies are at particularly high risk for high stoma output and pouching difficulties. High stoma output is more likely when the stoma is proximal to the terminal ileum, as is the case for a loop ileostomy proximal to an ileoanal pouch, or a more proximal loop ileostomy in obese patients with thick abdominal walls and thick, foreshortened mesenteries that technically preclude the use of the terminal ileum. Patients with loop
ileostomies are more likely to experience pouch leakage due to the more liquid output of ileostomies, as well as the conformation of the proximal os, which may not be as centered as the os of an end ileostomy. An inferior tilt of the proximal os, especially combined with stomal retraction, causes the stoma effluent to run under the lip of the stoma appliance. Pouch leaks can lead to maceration of the peristomal skin, further aggravating the problem. We discuss the management of these complications in the next section.

CLOSURE OF LOOP ILEOSTOMY

Closure of a loop ileostomy is usually performed at least 3 months after its creation, provided that imaging studies confirm that the distal pathology has resolved, or the colorectal anastomosis is patent and intact. While closing a loop ileostomy sooner than that may be feasible, some patients may still have dense scar tissue around the stoma. Dense adhesions increase the risk for injury to the small bowel or mesentery, and the need for laparotomy. Placement of an anti-adhesion barrier such as Seprafilm around the ileostomy at the time of its creation may reduce these risks.

Make a circumferential incision around the stoma, leaving a 3-mm rim of skin for retraction (Fig. 15-30). Sharply dissect the ileal loop free of the subcutaneous tissues and fascia. After completely mobilizing the bowel, carefully sweep around the anterior abdominal wall to check for additional adhesions, being mindful of the risk of inadvertent injury to small bowel. Successful mobilization of the ileostomy can usually be accomplished through the stoma defect (Fig. 15-31). However, some cases with dense adhesions may require a laparotomy, especially if injuries to the small bowel have occurred. The everted end of the bowel can be straightened with sharp dissection (Fig. 15-32). Infuse Betadine using a bulb syringe into the proximal and distal limbs of the loop ileostomy to detect serosal or full-thickness defects. Close any partial- or full-thickness defects transversely with interrupted 3-0 Vicryl sutures. If there are extensive bowel wall injuries, it may be necessary to resect a segment of small bowel.
**FIGURE 15-30** Make a circumferential incision around the ileostomy in the peristoma skin.

**FIGURE 15-31** Mobilize the ileostomy through the stoma defect.
Unevert the proximal limb of the bowel with sharp
dissection, and check for any partial- or full-thickness defects of the bowel
wall.

A sutured closure involves closing the defect in the antimesenteric bowel
wall transversely with 3-0 Vicryl seromuscular sutures (Figs 15-33 and 15-
34). A second layer of Lembert sutures may be used for reinforcement. If
there is a size discrepancy between the proximal and distal limbs, then make
a Cheatle incision on the antimesenteric bowel wall of the smaller side. If a
small bowel resection was necessary, then perform a handsewn end-to-end
anastomosis by approximating the mesenteric side of the bowel with
interrupted sutures of 3-0 Vicryl that are full-thickness through the bowel
wall, making sure that the mucosa is tucked into the lumen. Close the
antimesenteric side of the bowel with interrupted seromuscular sutures of 3-0
Vicryl. In either case, the stapled option involves firing a linear cutting
stapler down the proximal and distal lumens, creating a side-to-side
anastomosis (Fig. 15-35). Fire a linear stapler to close the end of the
anastomosis (Figs 15-36 through 15-39). Closure of the defect is as described
for colostomy site closure.
FIGURE 15-33 Suture the defect closed in a transverse fashion.

FIGURE 15-34 One or two layers of 3-0 Vicryl sutures are typically used.
**FIGURE 15-35** A stapled side-to-side anastomosis is an option for ileostomy closure. Fire a linear cutting stapler down both lumens.

**FIGURE 15-36** The linear stapler creates a side-to-side anastomosis. Check the staple line for bleeding.
FIGURE 15-37 Offset the linear staple lines before closing the end of the anastomosis.
FIGURE 15-38 Close the end of the anastomosis with a linear stapler.

FIGURE 15-39 Side-to-side stapled anastomosis.

Loop-End Ileostomy

INDICATIONS

A loop-end ileostomy is a good alternative to end ileostomy in the case of a thick abdominal wall or a foreshortened small bowel mesentery that prevents the end of the small bowel from reaching through the stoma defect. It is far better to create a loop-end ileostomy that is adequately everted than to create a suboptimal end ileostomy that is retracted or ischemic, resulting in pouching difficulties.

TECHNIQUE

A loop-end ileostomy is created by first determining the most distal loop of small bowel that will reach through the abdominal wall. Place an umbilical tape through a defect in the mesentery at its junction with the bowel wall. Place orienting sutures marking the proximal and distal bowel (Fig. 15-40). Oversew the distal end of the bowel (Fig. 15-41). Create the stoma defect and bring the loop through the defect using the guidance of an umbilical tape or Penrose drain after wrapping the bowel with an adhesion barrier if the stoma is temporary (Fig. 15-42). Place a stoma rod through the defect in the mesentery where the umbilical tape was (Fig. 15-43). Transversely incise the distal side of the loop. Evert the proximal side by placing three-point sutures
full-thickness through the bowel wall edge, seromuscular through the bowel wall at the level of the skin, and through the dermis. To mature the distal side, place two-point sutures full-thickness through the bowel wall edge, and through the dermis (Fig. 15-44).

**FIGURE 15-40** Find the most distal loop of small bowel that will reach through the abdominal wall and place orienting sutures to mark the proximal and distal bowel.

**FIGURE 15-41** Oversew the distal staple line.
FIGURE 15-42 Bring the loop of ileum through the stoma defect.

FIGURE 15-43 Place a stoma rod through the mesentery at its junction with the bowel wall.
FIGURE 15-44 Mature the loop-end ileostomy by incising the distal side of the loop transversely and everting the proximal side (inferior in this figure) using three-point sutures of 3-0 Chromic.

**Separated Ileostomy (Divided End-Loop)**

**INDICATIONS**

A separated ileostomy is useful in situations where complete fecal diversion is necessary, or if there is difficulty in bringing enough bowel through the abdominal wall.
**TECHNIQUE**

Divide the ileum with a linear cutting stapler, taking care to preserve all mesenteric vessels (Fig. 15-45). Create the stoma defect. Bring the proximal limb and the antimesenteric corner of the distal limb through the stoma defect (Fig. 15-46). Excise the antimesenteric corner of the distal limb and remove the end of the proximal limb (Fig. 15-47). Mature the proximal side using three-point sutures and the distal corner using two-point sutures (Fig. 15-48).

**FIGURE 15-45** Preserve the mesenteric blood supply when dividing the bowel.
FIGURE 15-46 Bring the proximal limb through the stoma defect, as well as the antimesenteric corner of the distal limb. In this figure, the proximal limb is inferior and the distal limb is superior but this configuration is not mandatory.
FIGURE 15-47  Remove the staple line of the proximal limb (inferior in this figure) and the antimesenteric corner of the distal limb (superior in this figure).

FIGURE 15-48  Mature the proximal limb (inferior in this figure) of the bowel by everting it with three-point sutures. The bowel edges of the
proximal and distal limbs that are adjacent to each other should be sutured to each other, and the rest of the distal limb should be sutured to the dermis of the stoma defect.

Ileostomy Care and Skin Complications

A well-placed and well-constructed ileostomy should offer the patient a good quality of life, minimal restrictions on activity, and ability to enjoy a range of foods. Most patients use a two-piece ileostomy appliance system comprised of a faceplate with a skin barrier and a pouch. The stoma opening of the skin barrier must match the exact size of the ileostomy, so that all the peristomal skin remains protected from the ileostomy effluent. The faceplate typically lasts 3 to 5 days, but if the patient experiences leakage under the appliance, then it requires more frequent changes. Maintaining a good seal around the ileostomy is crucial for maintaining the integrity of the peristomal skin and quality of life. The chemical dermatitis caused by leakage of ileostomy contents onto the skin can be extremely painful and results in a vicious cycle in which maintaining an adequate seal between the faceplate and macerated skin is impossible, leading to more leaks and skin trauma.

A retracted ileostomy with an os at skin level, or a tilted ileostomy with an os pointing down, is likely to result in leaks and pouching problems. Loop ileostomies are more likely to be associated with pouching problems because the distal opening is flush with the skin, allowing mucus to seep under the faceplate and disrupt the seal.

Management of High-Output Ileostomies

Many postoperative patients with new ileostomies experience a large volume of liquid output in the first few weeks after the operation. The daily volume of ileostomy output may be over a liter shortly after ileostomy creation, but should slow down to 500 to 800 mL after the small bowel has had a chance to adapt and increase its absorptive capacity. However, some patients may persistently have high output for various reasons including partial obstruction, short gut syndrome, or intrinsic bowel abnormalities.

The two main problems with high-output ileostomies are dehydration often accompanied by electrolyte abnormalities and pouching difficulties due
to the liquidity and volume of the effluent. The first step in the diagnostic workup is to rule out an underlying obstruction, which can cause the bowel proximal to the obstruction to secrete large volumes of fluid. Assess for an obstruction at the level of the fascia by inserting a finger into the stoma. A contrast study or ileoscopy through the ileostomy will demonstrate a more proximal obstruction.

Other possible etiologies include enteritis, short bowel syndrome, or inflammatory bowel disease. Most commonly, high ileostomy output is attributable to dietary indiscretion, and can be managed with a combination of diet changes, fiber supplementation, and medications. General principles for managing high ileostomy output are avoidance of concentrated sugars, hydrating with a combination of water and electrolyte beverages, and eating foods with a balance of protein, healthy fats, and soluble fiber (Table 15-4). Patients should be cautioned against drinking large amounts of water in an effort to keep up with the high volumes of watery ileostomy output they are experiencing, as this is may exacerbate electrolyte deficiencies and will not help to slow the output. Rather, they should be counseled to eat as well as hydrate with a diluted electrolyte drink.

**TABLE 15-4: MANAGEMENT OF HIGH ILEOSTOMY OUTPUT**
Fiber supplementation in the form of the soluble fiber pectin, powders dissolved in drinks, and fiber wafers are more effective than fiber pills. Medications such as loperamide, diphenoxylate-atropine, and tincture of opium can also be helpful in reducing the stoma output. Introduce one drug at a time and increase the dose as needed. Patients with fast transit may not absorb capsules or tablets, so elixir or orally disintegrating formulations may be more effective.

If all of these measures are unsuccessful at controlling the output and dehydration with electrolyte and/or nutritional deficiencies continues to occur, then the patient may require long-term parenteral replacement of fluids and electrolytes. Malnutrition due to poor absorption may require total parenteral nutrition.

Management of Ileostomy Obstruction

If a patient with an ileostomy develops obstructive symptoms, the first step is to rule out an obstruction due to a food bolus by irrigating the stoma with saline via a Foley catheter. Food particles in the irrigant raise suspicion of a food bolus as the culprit, and continued irrigation with warm saline should resolve the problem. If there are no food particles in the irrigant, then the
obstruction may be due to other causes such as adhesions, volvulus of small bowel around the ileostomy, or parastomal hernia. Cross-sectional imaging or a water-soluble contrast study via the stoma is helpful in making the diagnosis (Fig. 15-49).

**STOMA COMPLICATIONS**

**Parastomal Hernia**

Parastomal hernia occurs in up to 50% of patients. Risk factors of parastomal hernia include any condition that causes increased intra-abdominal pressure including obesity, chronic cough, chronic obstructive pulmonary disease, ascites, and straining behaviors. Other patient-related risk factors include older age, malnutrition, systemic steroids, and creation of the stoma during emergency operation. Technical factors that may reduce the risk of hernia are using an extraperitoneal route rather than a transperitoneal route, a smaller
trephine aperture for the stoma defect, and prophylactic mesh reinforcement of the stoma defect at the time of primary stoma creation.\textsuperscript{29,30} Most parastomal hernias may be managed nonoperatively, but complications associated with parastomal hernia such as pouching difficulty, bowel obstruction, or incarceration are indications for surgical repair (Figs 15-50 through 15-52). The best treatment for parastomal hernia repair is restoration of bowel continuity, as the recurrence rate of parastomal hernia repair with mesh is as high as 17% in some series.\textsuperscript{31} Primary suture repair has recurrence rates ranging from 46% to 100%, and there are few indications for this procedure. The use of biologic or prosthetic mesh is associated with a low incidence of mesh infection. Several options for mesh placement and surgical approach exist. An onlay mesh with a central defect for the stoma sits on top of the fascia. A sublay mesh with a keyhole opening for the stoma sits between the rectus muscle and the posterior rectus sheath. An underlay mesh sits posterior to the peritoneum. It may have a keyhole defect for the stoma opening, or it can be placed as a patch over the most distal intraperitoneal part of the colon. This Sugarbaker technique creates a short tunnel for the distal colon and has been found to have a lower recurrence rate.\textsuperscript{31} The final option is stoma relocation with mesh repair of the other stoma defect. The success of stoma relocation is equivalent to that of mesh repair.\textsuperscript{32}

\textbf{FIGURE 15-50} Patient with a large parastomal hernia, with pouching difficulties.
FIGURE 15-51  This parastomal hernia was causing recurrent bowel obstructions due to the incarcerated loops of bowel in the hernia sac.

FIGURE 15-52  Recurrent bowel obstructions and pouching difficulties are indications for parastomal hernia repair.
**Stoma Prolapse**

Loop colostomies using the sigmoid or transverse colon have the highest risk of stoma prolapse. An accompanying parastomal hernia is common. If the prolapse is incarcerated but the bowel is not ischemic, then manual reduction should be attempted immediately. If the stoma is edematous, pour a generous amount of sugar onto the prolapsed segment and allow it to sit for at least 10 minutes. The sugar will induce an osmotic diuresis of the bowel wall, thus reducing the edema and increasing the chances of a successful reduction. Place a gauze sponge over the prolapsed bowel and apply gentle constant pressure to the os of the stoma. Giving the patient pain medication or muscle relaxant may aid in this process as well. If manual reduction is successful, then the patient may undergo elective repair.

Inability to reduce the stoma or ischemic bowel is an indication for emergent surgical intervention. Operative approach depends on whether the ischemia extends below the fascia. Most cases of incarcerated and ischemic stoma prolapse require resection of the prolapsed segment using the existing stoma site, with creation of a new stoma. A laparotomy is necessary if operating through the stoma site does not allow adequate access for resection of the ischemic bowel segment, or adequate mobilization of proximal bowel for a new stoma. Other indications for surgical management for a prolapsing stoma include pouching difficulty, obstruction, and pressure necrosis or bleeding due to a traumatized stoma.

**Stomal Retraction**

Stoma retraction occurs when the bowel wall pulls away from the skin, causing the os of the stoma to sit below skin level. Risk factors for stomal retraction include inadequate mobilization of the bowel at the time of initial stoma creation, a thick abdominal wall, a short mesentery, and emergency surgery. This complication often occurs in the early postoperative period. If it occurs within a week of the initial operation, then it is worth considering reoperation for stoma revision to avoid the long-term sequelae associated with retraction. If it occurs more than a week from the time of initial operation, then reoperation may be ill-advised due to dense postoperative adhesions that are likely to preclude the additional mobilization that is needed to fix the problem. It is important to determine whether the bowel has
retracted below the fascia, as retraction below the fascia may cause intra-abdominal stool spillage and is an indication for operative intervention. If one encounters obliteratorive adhesions that preclude mobilization of the bowel, then a safer surgical strategy may involve bringing up a proximal loop stoma in a separate location.

If stoma retraction occurs too far after the initial operation to safely reoperate, and the distal end of the stoma is above the level of the fascia, then the mainstay of management is pouching strategies that will minimize damage to the peristomal skin and maintain a seal (Fig. 15-53).

**FIGURE 15-53** This patient had a retracted ileostomy that was very difficult to pouch, and as a result had caused significant peristomal skin irritation.

Prevention of stoma retraction involves mobilizing adequate bowel length at the time of initial stoma creation. As it may be very difficult to mobilize enough bowel and mesentery to bring the end of the bowel through a thick abdominal wall, especially if the mesentery is thick and foreshortened, a loop-end stoma can often be a good alternative that will reach through the abdominal wall without tension.

**Stoma Ischemia**

Risk factors for ischemia of the stoma include a thick abdominal wall, small stoma defect size relative to the bowel caliber, and excessive dissection or tension of the mesentery. The bowel wall may not demonstrate obvious signs
of ischemia until several days after the operation. Similar to the case of stoma retraction, it is important to determine whether the ischemia extends below the fascia. If the ischemia only involves the bowel above the fascia, then the ischemic mucosa will slough off with time, and usually does not require reoperation (Fig. 15-54). Ischemia extending below the fascia is an indication for operative intervention. If the cause of ischemia is a tight stoma defect, then a local stoma revision to increase the size of the defect and bring up a healthier segment of bowel may be successful. Laparotomy will be necessary if mobilization of additional bowel cannot be performed through the stoma site. Often a loop-end stoma is necessary to preserve adequate mesenteric blood flow in the setting of a thick abdominal wall and a short mesentery.

![Stoma with Mucosal Ischemia](image)

**FIGURE 15-54** This stoma has mucosal ischemia that did not extend past the fascia, and therefore did not require reoperation.

**Stoma Stenosis**

Stoma stenosis often occurs in conjunction with stomal retraction, which allows the skin of the stoma defect to close concentrically over the os. The most effective way to manage stoma stenosis is surgical revision, but patients who cannot undergo operative intervention may undergo stoma dilations.
Dilations can be performed in the office setting or under sedation in the operating room, depending on the patient’s comfort level.

**Mucocutaneous Separation**

Mucocutaneous separation, when the edge of the bowel wall separates from the skin edge at the border of the stoma, occurs as a result of poor wound healing (Fig. 15-55). The crevice that is formed by the separation presents a challenge for pouching, and patients may find it difficult to maintain an intact seal around the stoma. The key elements to managing this complication are to keep the peristomal skin in good condition, optimize nutrition, and to employ local wound care techniques to fill in the trough and induce granulation of the wound.

![FIGURE 15-55](image) This patient had underlying disease that precluded wound healing, and this led to severe mucocutaneous separation of the ileostomy.

**CONTINENT ILEOSTOMY**

Continent ileostomy (Kock pouch) was introduced in 1969 and gained popularity throughout the 1970s. Since the introduction of ileal pouch-anal anastomosis (IPAA), fewer continent ileostomies are being constructed because of their high complication and revision rates compared with IPAA. Patients with medically refractory ulcerative colitis or familial adenomatous polyposis may still choose to have a continent ileostomy, often after having complications from IPAA that cannot be salvaged, or if end ileostomy presents particular challenges. Many patients who pursue continent ileostomy do so because of psychosocial considerations, and feel strongly
that their quality of life will be significantly improved, even with the potential of multiple complications. Contraindications for continent ileostomy include inability to learn how to reliably intubate the pouch, personal or family history of desmoid disease given the risk for multiple operations and thus surgical trauma, obesity due to the increased risk for valve slippage, and inadequate small bowel length. Continent ileostomy should only be offered to highly motivated and well-informed patients who understand the high risk for reoperation and pouch failure.

Several techniques for creating continent ileostomies have been described. The original Kock pouch design has been modified into a three-limbed S-pouch with a nipple valve created by intussuscepting a segment of the efferent limb. First, three 10- to 12-cm segments of small bowel are measured out and sutured together in an S-configuration, making sure to leave an additional 14 to 16 cm of small bowel distal to the pouch for the valve and outlet (Fig. 15-56). The antimesenteric side of all three limbs is opened with a longitudinal enterotomy. Another layer of sutures is placed in the back wall (Fig. 15-57). Intussusception of 6 cm of the efferent limb into the pouch forms the nipple valve (Figs 15-58 through 15-60). Before intussuscepting the bowel, the peritoneum of the small bowel mesentery is stripped, and cross-hatches in the mesentery can be created with electrocautery. These two techniques induce scar formation to hold the intussusception in place. The intussusception is fixed in place by firing a linear noncutting stapler along the length of the valve on either side of the mesentery (Fig. 15-61). The anterior wall of the pouch is closed in two layers. Before completing closure, the valve is fixed to the wall of the pouch with a third fire of the linear noncutting stapler. The valve’s continence is tested after closure of the pouch by inserting a Medena catheter through the valve, infusing saline to fill the pouch, and removing the tube and ensuring that there is no leakage of saline from the pouch. Additional sutures are placed around the base of the valve where it enters the pouch, to further secure it from slipping. These sutures are used to affix the pouch to the abdominal wall at the planned stoma site (Fig. 15-62).
FIGURE 15-56 Three 10- to 120-cm segments of small bowel are sutured together in an S-configuration.
FIGURE 15-57  The antimesenteric sides of the S-configuration are opened, and a second layer of sutures is placed in the back wall of the pouch.
FIGURE 15-58 Intussusception of a 6-cm segment of the efferent limb (distal to the pouch) forms the nipple valve.
FIGURE 15-59 The intussusception creates a continent valve.

FIGURE 15-60 Intussuscepted nipple valve in a case of Kock pouch revision.
FIGURE 15-61 The intussusception is stabilized by firing a linear noncutting stapler along the valve on either side of the mesentery.

FIGURE 15-62 Affix the pouch to the abdominal wall using sutures that have been placed around the base of the valve.

The site of a continent stoma is usually more inferiorly located than a
conventional ileostomy site. This allows the pouch to sit in the pelvis, and also allows the stoma site to be concealed below the beltline. The remaining length of distal small bowel is brought through the site, and a skin-level stoma is created by suturing the bowel wall to the dermis without eversion (Figs 15-63 and 15-64). A straight path for intubation from the stoma through the valve and into the pouch is paramount for a good functional outcome and minimizing the risk for repeated trauma to the valve or pouch from intubation (Fig. 15-65). Before abdominal wall closure, the ease of intubation and continence of the pouch is tested. The catheter remains in place within the pouch with regular irrigations for at least 2 weeks after the operation. Patients will then intubate every 2 hours for another week, then increase the time interval gradually until they are intubating every 4 to 6 hours.

FIGURE 15-63 The stoma is brought through the stoma defect, which is located more inferiorly than a traditional ileostomy.

FIGURE 15-64 The stoma is matured without eversion to create a skin-level stoma.
A Medena catheter is typically used to intubate the stoma. It is important to ensure that there is a straight path from the stoma, through the valve, and into the pouch. The Barnett Continent Ileostomy Reservoir is another method of continent ileostomy construction in which an antiperistaltic segment of the efferent limb is used to create the valve and stoma. A segment of blind-ending efferent bowel coming off the pouch wraps around the valve, creating a living collar that distends as the pouch fills, thus closing off the valve. The afferent limb of bowel attaches to the apex of the pouch. The T-pouch design was first used as a continent neobladder, and subsequently adopted for continent ileostomy. This design also uses a separate segment of bowel to form the valve, but instead of intussusception, the valve consists of an antireflux mechanism using an ileal tunnel. The pouch is constructed of two limbs of small bowel. The antimesenteric side of the bowel is opened, and the edges along the valve are closed over the valve.
to form the ileal tunnel. The reservoir is then folded in half to close it.

Patients who have a well-functioning continent ileostomy enjoy excellent quality of life. Most patients intubate the pouch every few hours, depending on the volume of the output. Irrigation may be necessary depending on the consistency of the output.

Early postoperative complications include leakage or bleeding from suture lines, or valve necrosis. Late complications include valve slippage, stomal stenosis, pouchitis, volvulus, and fistulas (Fig. 15-66). About 50% of patients will require at least one reoperation for revision of the pouch or excision of the pouch. Valve slippage can present as incontinence to gas or stool, or difficulty with intubation. Endoscopy confirms the diagnosis. Inability to intubate a still-continent pouch results in an obstruction, and decompression with endoscopy with placement of a catheter is the temporary treatment until surgical correction. Surgical management of a slipped valve or a valve fistula usually requires construction of a new valve using the efferent length of bowel just proximal to the pouch, 180-degree rotation of the pouch, and anastomosis of the new efferent bowel end to the opening where the old valve was (Figs 15-67 through 15-69). The highest rate of pouch reoperation is in the first 2 years, but in those patients in whom the pouch was salvaged, long-term durability and satisfaction were high.41 Patients undergoing revision of a continent ileostomy must understand that the risk of pouch excision and conversion to a conventional ileostomy is very high—at least 50%. Many patients who face the chance of losing an imperfectly functioning continent ileostomy will prefer to live with incontinence rather than take the chance of losing the pouch completely.
Late complications of continent ileostomy include fistula and valve slippage. Valve slippage presents as incontinence or difficulty with intubation.
FIGURE 15-67 Revision of a continent ileostomy for a slipped nipple valve can be performed by using the afferent segment of bowel for a new nipple valve. The ileum is transected about 12 to 15 cm proximal to the pouch.
FIGURE 15-68 The pouch is rotated 180 degrees and the bowel is intussuscepted to form a new valve. The site where the old valve was is sutured to the proximal ileum.
FIGURE 15-69 The valve is stapled and the pouch is completed in the same way as a new continent ileostomy.

APPENDICOSTOMY

Appendicostomy with antegrade continence enema is an option for patients with fecal incontinence or medically refractory constipation due to colonic inertia. The cecum is plicated around the base of the appendix as an antireflux mechanism. The appendix is brought up to the umbilicus and the tip opened to create an inconspicuous stoma. The appendicostomy is intubated once a day for administration of an antegrade enema to clear the colon. In the long term, most patients experience improvement in symptoms but there is wide variety among studies.\textsuperscript{42,43} It is not a commonly performed procedure, but may be successful for carefully selected highly motivated patients. Complications include stenosis of the stoma and leakage from the appendicostomy. A significant proportion of patients do not benefit from this operation so will need another operation to address the underlying problem.
CONCLUSION

Intestinal stomas, if well-formed and well-placed, are compatible with a good quality of life for most patients, allowing them to return to normal activities. However, poorly constructed stomas, high-output stomas, and stomas located in suboptimal sites on the abdominal wall are associated with pouching difficulties, appliance leaks, skin breakdown, and poor quality of life. In many cases, a temporary or permanent stoma may be a major improvement to quality of life. For example, patients with severe medically-refractory inflammatory colitis usually find that having an end ileostomy is far superior to suffering with frequent, painful bloody bowel movements. In the decision-making processes that involve choices between options that result in a permanent stoma versus options that result in intestinal continuity, patients must be counseled that intestinal continuity does not always equal a better quality of life than a permanent stoma. For example, patients undergoing operations for distal rectal cancer may find that a low pelvic anastomosis is extremely disruptive due to clustering of bowel movements, frequency, and urgency. In severe cases, a permanent colostomy may be preferable. Specific scales to measure quality of life associated with a stoma have been developed, which will allow for more robust assessment of quality of life in future studies. Surgeons must engage patients in a shared decision-making process to help make treatment decisions that will offer optimal quality of life outcomes.

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ABDOMINAL ABSCESS AND ENTERIC FISTULAE
Joao B. Rezende Neto • Jory S. Simpson • Ori D. Rotstein

ABDOMINAL ABSCESS

Definition and Etiology

Abdominal abscesses are well-defined collections of infected purulent material that are walled off from the rest of the peritoneal cavity by inflammatory adhesions, loops of intestine and their mesentery, the greater omentum, or other abdominal viscera. Abscesses may occur in the peritoneal cavity, either within or outside of abdominal viscera (extravisceral), as well as in the retroperitoneum.¹ Most relevant to the surgeon are extravisceral abscesses that usually arise in 1 of 2 situations: (1) after resolution of diffuse peritonitis in which a loculated area of infection persists and evolves into an abscess and (2) after perforation of a viscus or an anastomotic breakdown that is successfully walled off by peritoneal defense mechanisms. More than 80% of intra-abdominal abscesses occur in the postoperative period, the majority of which occur after pancreaticobiliary or colorectal surgery and are
usually related to anastomotic dehiscence.\textsuperscript{2,3}

Occasionally, postsurgical abscesses result from infection of an intraperitoneal hematoma that develops following surgery. Less frequently, intra-abdominal abscesses are unassociated with previous surgery and are usually attributable to spontaneous inflammatory processes associated with a small, localized perforation, such as in appendicitis, diverticulitis, and Crohn disease.\textsuperscript{3,4} Visceral abscesses are most commonly caused by hematogenous or lymphatic spread of bacteria to the organ. Retroperitoneal abscesses may be caused by several mechanisms, including perforation of the gastrointestinal (GI) tract into the retroperitoneum and also hematogenous or lymphatic spread of bacteria to the retroperitoneal space, where seeding of uninfected collections such as peripancreatic necrosis or hematomas may occur.

**Pathophysiology of Abscess Formation**

After bacterial contamination of the peritoneal cavity, a complex series of events is initiated that, under ideal circumstances, effects complete eradication of invading bacteria. The 3 major defense mechanisms in the peritoneal cavity are (1) mechanical clearance of bacteria via the diaphragmatic lymphatics, (2) phagocytosis and destruction of suspended or adherent bacteria by phagocytic cells, and (3) sequestration and walling off of bacteria coupled with delayed clearance by phagocytic cells.\textsuperscript{5} The first 2 mechanisms act rapidly, usually within hours. Egress of bacteria from the peritoneal cavity via the lymphatics is responsible for the early septic response due to bacteremia and initiation of the innate immune response to infection.

The initial peritoneal response to bacterial contamination is characterized by hyperemia, exudation of protein-rich fluid into the peritoneal cavity, and a marked influx of phagocytic cells. Resident peritoneal macrophages predominate early in the infection, but the rapid influx of neutrophils after a 2- to 4-hour delay makes them the predominant phagocytic cell in the peritoneal cavity for the first 48 to 72 hours.\textsuperscript{6} The combination of resident peritoneal cells plus the migration of these cells into the peritoneum serves to propagate the initiation of the innate immune response, including the elaboration of inflammatory cytokines and the procoagulant response. In
humans with severe intra-abdominal infection, peritoneal levels of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6 are higher than levels measured simultaneously in plasma.\textsuperscript{7,8} Haecker and colleagues reported that TNF-α and IL-10 levels are increased and reach 100- to 1000-fold in the plasma following appendiceal perforation. In adult patients, a correlation between the magnitude of the cytokine response and outcome in infected patients has been demonstrated in several clinical studies.\textsuperscript{9} Higher levels of circulating TNF-α and IL-6 have been recorded in patients who later die with intra-abdominal infection.\textsuperscript{7} Interestingly, elevated peritoneal levels persist even after systemic inflammatory response has abated. This suggests that during resolving peritonitis, there is compartmentalization of the response with local cytokine elaboration, thereby promoting local resolution of infection.

Other cell types are likely important in the initiation of the local peritoneal response. Peritoneal mast cells and mesothelial lining cells have also been shown to be potent producers of a range of cytokines and procoagulants. Fibrin deposition appears to play an important role in this compartmentalization of infection, not only by incorporating large numbers of bacteria within its interstices\textsuperscript{10} but also by causing loops of intestine to adhere to each other and the omentum, thereby creating a physical barrier against dissemination. Fibrin deposition is initiated after the exudation of protein-rich fluid containing fibrinogen into the peritoneal cavity. The conversion of fibrinogen to fibrin is promoted by the elaboration of tissue factor by both mesothelial cells and stimulated peritoneal macrophages.\textsuperscript{11} In addition, generation of other inflammatory mediator molecules and components of the complement cascade (eg, C3a and C5a) further promotes the development of local inflammation. The net effect of these responses is the localization of the bacterial infection in the peritoneal cavity, wherein ultimate resolution can occur. However, a number of local factors thwart complete resolution and presumably establish the local environment for persistent infection and hence abscess formation. These include regional fibrin deposition that impedes phagocytic cell migration, factors that inhibit phagocytic cell function such as hemoglobin, particulate stool, low pH, and hypoxia.

On the microbial side, polymicrobial flora of these infections as well as the near ubiquitous presence of \textit{Bacteroides fragilis} and its unique capsular
polysaccharide have been implicated in persistence of infection and abscess formation. Considered together, while the process of abscess formation represents a successful outcome of the peritoneal response to bacterial contamination of the peritoneal cavity, one is left with a residual infection that carries with it morbidity and potential mortality and must be actively managed.

Clinical Presentation and Diagnosis

Clinical Presentation

Diagnosis of an intra-abdominal abscess is based on clinical suspicion complemented by radiologic confirmation of the presence of the abscess. High spiking fevers, chills, tachycardia, tachypnea, and leukocytosis, associated with localized abdominal pain, anorexia, and delay in return of bowel function in the postoperative patient, are the classic signs and symptoms associated with the presence of an intra-abdominal abscess. The presence of a well-localized tender mass on clinical examination is consistent with the presence of an abscess. However, there may be considerable variability in the clinical appearance of the patient with this infection, ranging from a relatively mild picture where the patient appears generally well but is “slow to recover” from his or her surgical procedure to those who manifest evidence of profound systemic inflammation. There may be no mass palpable on clinical examination. A number of factors may contribute to this variability, including patient factors such as age, immunocompetence, and concurrent use of antimicrobials, as well as abscess factors such location and size of the abscess and how well walled off the abscess is. For example, subphrenic abscesses can present with vague upper quadrant abdominal pain, referred shoulder pain, and occasionally hiccoughs but with no localized abdominal tenderness or palpable mass. By contrast, paracolic abscesses present with localized tenderness and may manifest as a palpable mass on abdominal examination. Pelvic abscesses may also cause local irritation of the urinary bladder, causing frequency, or of the rectum, resulting in diarrhea and tenesmus. Retroperitoneal collections, particularly psoas abscesses, can manifest as leg and back pain with muscular spasm and flexion deformity of the hip. In reality, with the ready availability of computed tomography (CT) scanning in most institutions, almost any deviation from the normal recovery
trajectory in the postoperative period will prompt a CT scan and possible early detection of the abscess.

**DIAGNOSTIC TESTS**

Imaging provides the definitive evidence of the presence of an intra-abdominal abscess. Abdominal plain films can be helpful in identifying air-fluid levels in the upright or decubitus positions, extraluminal gas, or a soft tissue mass displacing the bowel. In the postoperative patient, however, extraluminal gas may be present for up to 7 days. Overall, plain radiography may suggest the presence of an abscess, but other imaging modalities have essentially replaced plain films in the evaluation of intra-abdominal abscesses.

CT scanning has emerged as the radiologic investigation of choice in the diagnosis of intra-abdominal abscess. With its ready availability, it has essentially supplanted abdominal ultrasound (US) as the main diagnostic tool in this setting, mainly because of its accuracy, but also because its functionality is not impaired in the setting of ileus, wound dressings, stomas, and the open abdomen. The accuracy of the scan is improved if contrast is used. Intravenous contrast increases the accuracy of defining the presence of an abscess, while GI tract contrast helps to distinguish fluid-filled bowel loops from an abscess and, in addition, may detect the presence of an anastomotic leak. In a retrospective study that compared US and CT in diagnosing intra-abdominal abscesses, the sensitivity of US in 123 patients was 82% compared to 97% in 74 patients by CT, and the overall accuracy of US was found to be 90% versus 96% for CT.

Criteria for identification of an abscess by CT have been well described and include identification of an area of low CT attenuation in an extraluminal location or within the parenchyma of solid abdominal organs. The density of abscesses usually falls between that of water and solid tissue. Other radiologic signs of an abscess are mass effect that replaces or displaces normal anatomic structures, a lucent center that is not enhanced after the intravenous administration of a contrast medium, enhancing rim around the lucent center after IV contrast administration, and gas in the fluid collection (Fig. 16-1).
One of the major advantages of CT over US is the ability to detect abscesses in the retroperitoneum and pancreatic area. There are also some disadvantages to CT scanning. In the absence of contrast rim enhancement, gas, or visible septations, CT cannot distinguish between sterile and infected fluid collections. Occasionally, there may be a solid-appearing collection that is really an abscess with a high leukocyte and protein content. Septations and other signs of loculated abscesses can often be better visualized with US than CT. Finally, CT scanning is sometimes unable to differentiate between subphrenic and pulmonic fluid, a relatively common situation in abdominal surgery. In these limited circumstances, US may be considered as a complement to CT imaging.

Other modalities include magnetic resonance imaging (MRI). While MRI can sometimes better delineate the extent of an abscess, particularly in relation to adjacent soft tissue structures such as muscles and major blood vessels, it does not clearly have advantages over CT scanning and its practicality may be limited in the sick surgical patient. One area where US
and MRI may be relevant is in the investigation of the pregnant patient with abdominal pain.\textsuperscript{17} US is particularly useful when appendicitis/appendiceal abscess is suspected, and MRI may be useful when localization is less clear. The roles of radiolabelled compounds in the diagnosis of abdominal abscesses are limited at present.\textsuperscript{18}

**Management**

The basic principles underlying the successful treatment of intra-abdominal abscesses are three fold:

1. Adequate resuscitation and support
2. Antimicrobial therapy
3. Source control/abscess drainage

**RESUSCITATION AND SUPPORT**

In keeping with the variable presentation of patients with intra-abdominal abscesses, the initial approach to resuscitation and support will vary considerably. Attention to the ABCs (airway, breathing, circulation) while individualizing the intervention for each patient according to his or her deviation from normal physiology is appropriate. Particularly in the postsurgical patient, nutritional support should be considered.

When feasible, oral nutrition should be given in preference to total parenteral nutrition. Some patients are able to ingest food and/or supplements by mouth, while others might require an enteral feeding tube, due to anorexia, precluding adequate ingestion of nutrients. Systematic review of the literature suggests that infectious complications and cost are reduced in critically ill patients receiving enteral nutrition compared to parenteral nutrition.\textsuperscript{19} One can presumably extrapolate to patients with intra-abdominal infection. When abscess formation occurs due to an anastomotic leak, there is a sense that this might preclude use of enteral nutrition. This concern is likely unfounded, unless there is profound ileus associated with the infection.

**ANTIMICROBIAL THERAPY**

Considerations regarding antimicrobial use are based on the microbial flora
recovered from the infections. Over the past decade, there has been increasing appreciation that there is an evolution of the flora with increasing severity of abdominal infection. For example, Table 16-1 shows the bacteriology of peritonitis in patients with community-acquired peritonitis and those with postoperative peritonitis.

### TABLE 16-1: MICROBIOLOGY OF COMMUNITY-ACQUIRED PERITONITIS COMPARED TO HEALTH CARE–ASSOCIATED PERITONITIS

<table>
<thead>
<tr>
<th>Strain</th>
<th>Percent of Isolates of Community-Acquired</th>
<th>Percent of Isolates of Postoperative (Health Care–Associated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococci</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td><em>Enterobacter</em> sp</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td><em>Bacteroides</em> sp</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td><em>Klebsiella</em> sp</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Coagulase-negative staph</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><em>Candida</em></td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Streptococci</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Hemolytic strep</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>


The major pathogens in community-acquired intra-abdominal infections are coliforms (especially *Escherichia coli*) and anaerobes (especially *B fragilis*). As illustrated, while both are polymicrobial, postoperative peritonitis has a higher incidence of more resistant microbes. Aside from patients with postoperative peritonitis, other factors predict this shift in microbiology, including advanced age, severe physiologic derangement, immunosuppression, previous use of antibiotics, and residence in a health
Guidelines have been developed by the Surgical Infection Society and the Infectious Diseases Society of America regarding the use of antimicrobial therapy in intra-abdominal infection. These authors have risk-stratified patients into 3 categories and provided recommendations for empiric antimicrobial regimens according to category. The 3 categories are (1) community-acquired infections of mild to moderate severity; (2) high-risk or severe community-acquired infections; and (3) health care–associated infections. Factors that dictate conversion from mild-to-moderate severity to high severity include severe physiologic derangement (eg, high Acute Physiology and Chronic Health Evaluation II [APACHE II] score), advanced age, or immunocompromised state. Our institution follows the best practice in general surgery guidelines of the University of Toronto–affiliated hospitals (Table 16-2). Even though these guidelines are readily applicable to decision making regarding patients coming to the hospital with abscesses, they are not to be considered a meta-analysis subjected to formal peer review process. It is noteworthy that while Enterococcus is frequently recovered in isolates in these infections, the evidence demonstrates no additional benefit to treating this microbe as part of empiric therapy.

### Table 16-2: Recommendations for Antimicrobial Therapy in the Community-Acquired Setting
When possible, switchover to oral agents is appropriate. Traditionally, the duration of antibiotics was based on resolution of the clinical signs and symptoms of infection, a period that usually ranged from 4 to 7 days. Should there be no resolution by this time, reevaluation of the patient for the presence of persistent infection in the abdomen and elsewhere is appropriate. A clinical trial randomly assigned 518 patients with complicated intra-abdominal infections to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus with a maximum of 10 days, or to receive a fixed course of antibiotics of 4 ± 1 calendar days. Patients in both groups underwent adequate source control. The results of that study showed similar outcomes after fixed-duration antibiotics (approximately 4 days) compared to a longer course of antibiotics until the resolution of physiologic abnormalities (approximately 8 days). This study successfully challenged the paradigm that discontinuation be based on clinical signs of infection and suggests that a shorter fixed duration of treatment may be acceptable therapy.

Patients who present in the postsurgical period fall into the category of patients with health care–associated infection. In these patients, empiric therapy should include agents with expanded spectra against gram-negative...
aerobic and facultative bacilli, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Table 16-3 shows the considerations regarding selection depending on local institutional microbial isolates. Empiric anti-enterococcal treatment should be given. Treatment of *Candida* with fluconazole when recovered from cultures and treatment of methicillin-resistant *Staphylococcus aureus* with vancomycin should be followed if the patient is colonized with the microbe.

### Table 16-3: Recommendations for Alterations of Antimicrobial Therapy in the Health Care–Associated Setting

<table>
<thead>
<tr>
<th>Organisms Seen in Health Care–Associated Infection at the Local Institution</th>
<th>Carbapenem*</th>
<th>Piperacillin-Tazobactam</th>
<th>Ceftazidime or Cefepime, Each With Metronidazole</th>
<th>Aminoglycoside</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20% Resistant <em>Pseudomonas aeruginosa</em>, ESBL-producing Enterobacteriaceae, <em>Acinetobacter</em>, or other MDR GNB</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>ESBL-producing Enterobacteriaceae</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Not recommended</td>
<td>Recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> &gt;20% resistant to ceftazidime</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>MRSA</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

**Abbreviations:** ESBL, extended-spectrum β-lactamase; GNB, gram-negative bacillus; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*. **NOTE:** "Recommended" indicates that the listed agent or class is recommended for empiric use, before culture and susceptibility data are available, at institutions that encounter these isolates from other health care–associated infections. These may be unit- or hospital-specific.

*Imipenem-cilastatin, meropenem, or doripenem.*


### SOURCE CONTROL

*Source control* is a term used to include all physical measures taken to control a focus of infection. Here we focus our discussion to abscess drainage, but adequate source control may also include debridement of necrotic tissue, surgical repair, resection, and/or exteriorization of the anatomic defect causing peritoneal contamination.

Over the past 2 decades, percutaneous drainage of abscesses has become an established technique and a safe alternative to surgery. This evolution of care has not been based on a series of strong randomized trials showing equivalence or superiority of this approach. Rather, observational studies
from a number of centers have shown it to be a safe effective alternative to surgical intervention, with equivalent success rates, comparable mortality (10%-20%) and morbidity (~25%).\textsuperscript{24-26} Combined with other advantages of percutaneous approaches including avoidance of general anesthesia, lower costs, and the potential for fewer complications, it has now become the default approach to abscess management. Prerequisites for catheter drainage include an anatomically safe route to the abscess, a well-defined unilocular abscess cavity, concurring surgical and radiologic evaluation, and surgical backup for technical failure. Multiple abscesses, abscesses with enteric connections as seen with enterocutaneous fistulas, and the need to traverse solid viscera are not contraindications. Indeed, as the technique has evolved over several decades, the barriers to accessing unusually positioned collections have disappeared with the use of unconventional routes (transgluteal, transvaginal, transrectal) and the advent of new technologies including endoscopic US.\textsuperscript{27,28} Even the presence of septations and loculations has not precluded at least an attempt to use percutaneous drainage.\textsuperscript{29}

Percutaneous drainage can be performed with US or CT guidance. CT provides for more precise identification of organs and bowel loops and is more accurate for planning of drainage route.\textsuperscript{15} Once the abscess is identified, initial diagnostic aspiration should be sent for Gram stain and microbiological culture. The catheter used for drainage should be as small as possible for safety, yet large enough so that the tubing does not become obstructed. Most commonly used catheters range in size from 8 to 12 F. With appropriate catheter placement, the abscess cavity typically decompresses and collapses. Irrigation of the catheter should be done once daily to ensure tube patency. As catheter drainage decreases, repeat CT scanning can be performed to evaluate for residual contents. If drainage increases over time or continues at a steady rate, the development of an enteric fistula must be suspected. This may not have been unexpected when the catheter was initially placed near a perianastomotic abscess or an abscess adjacent to some underlying pathologic process. Potential complications of catheter placement include bacteremia, sepsis, vascular injury, enteric puncture, cutaneous fistula, and transpleural catheter placement.

Catheters should be maintained on closed drainage systems. There does not appear to be benefit to the use of suction or irrigation of these catheters, although flushing once per day with saline ensures patency. Patients should respond with defervesce of symptoms within 48 hours of catheter insertion. If
they do so, a repeat CT scan is done at approximately 5 to 7 days to ensure shrinkage of the abscess. Criteria for removal of the drain include (1) clinical resolution of septic parameters, including patient well-being, normal temperature, and leukocyte count; (2) minimal drainage from the catheter; and (3) CT evidence of the resolution of the abscess.

As noted previously, studies comparing outcomes of surgical and percutaneous drainage of intra-abdominal abscesses demonstrate comparable efficacy. In one study, patients were matched for age, abscess location, and etiology, and had similar APACHE II scores. There were no differences between percutaneous and surgical drainage in patient morbidity, mortality, or duration of hospital stay. Furthermore, initial percutaneous drainage of abscesses in the context of diverticular disease allowed for subsequent definitive operative resection and primary anastomosis in 1 rather than 2 operations. Another group retrospectively examined postoperative intra-abdominal abscesses after laparotomy. This study similarly demonstrated that use of either form of drainage resulted in similar cure rates for postoperative intra-abdominal abscesses.

With clear demonstration of its efficacy when compared to surgical drainage, percutaneous drainage should be considered the preferred approach in source control of abscesses. Table 16-4 shows outcome of percutaneous drainage according to underlying pathologic processes. In general, one should predict a successful outcome in patients with a single, well-defined abscess with no enteric communication. The presence of enteric communication per se does not reduce the likelihood of success as it is defined by the resolution of the infection. In a postoperative abscess, following drainage of the infection, the underlying anastomotic defect will usually close. In other settings, there may be a requirement for subsequent surgery to manage the underlying disease process such as diverticular disease or Crohn disease. For example, in one study, approximately 75% of patients with large peridiverticular abscesses were drained percutaneously and then they underwent a single-stage sigmoid colectomy. Other circumstances such as fungal abscesses, infected hematomas, peripancreatic necrosis, or necrotic-infected tumor have a lower success rate for percutaneous drainage and early consideration for surgical intervention. CT features such as the presence of a “rind,” a sharp exterior margin, air-fluid levels, and septations do not predict outcome and therefore should not be determinants as to whether or
not initial percutaneous drainage should be used. Finally, one should use clinical judgment as to the need for percutaneous drainage for small abscesses (<5-cm diameter) such as those that might occur with acute diverticulitis, Crohn disease, and interloop collections. These may respond well to antibiotics alone, and the use of percutaneous drainage may be meddlesome and potentially morbid.

<table>
<thead>
<tr>
<th>TABLE 16-4: DETERMINANTS OF OUTCOME FOLLOWING PERCUTANEOUS DRAINAGE OF ABSCESSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Condition</td>
</tr>
<tr>
<td>Single, well-defined bacterial abscess with no enteric communication</td>
</tr>
<tr>
<td>Abscess with enteric communication (eg, diverticular abscess or Crohn disease abscess)</td>
</tr>
<tr>
<td>Interloop abscess or other difficult-to-access abscesses (eg, deep pelvic)</td>
</tr>
<tr>
<td>Early postoperative diffuse peritonitis (eg, caused by anastomotic dehiscence or bile peritonitis)</td>
</tr>
<tr>
<td>Infected tumor mass</td>
</tr>
<tr>
<td>Fungal abscess</td>
</tr>
<tr>
<td>Infected hematoma</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
</tr>
<tr>
<td>Small abscess (&lt;4 cm in diameter)</td>
</tr>
</tbody>
</table>

There are circumstances where percutaneous drainage should be considered contraindicated. Most important among these is the circumstance where peritoneal infection is not localized, such as in the early postsurgical period where an anastomotic leak leads to diffuse peritonitis. Abdominal CT scans performed in this scenario may demonstrate 1 or more discrete fluid collections. When there is diffuse peritoneal irritation on clinical examination, fluid collections distant from the anastomosis, or the presence of massive intraperitoneal air, surgical intervention is clearly indicated. Attempts to manage such situations with percutaneous interventions invariably lead to delayed definitive surgical management and adverse outcome.

**SURGICAL DRAINAGE**

As stated previously, percutaneous drainage is the procedure of choice for the majority of intra-abdominal abscesses, with the caveats being those indicated.
Specifically, when the infection is diffuse rather than localized, surgical intervention is clearly indicated. Second, when the content of the abscess is too thick for percutaneous drainage, an initial percutaneous attempt may be reasonable, but conversion to surgery early in the course is reasonable. Finally, when access is impossible, surgery is indicated. This last circumstance is increasingly rare.

The transperitoneal approach allows for examination of the entire abdominal cavity and allows for the drainage of multiple abscesses. Subphrenic abscesses and right subhepatic abscesses may also be approached by lateral abdominal incisions. Once abscess cavities are identified, they are entered and drained quickly to minimize spillage and contamination of the rest of the peritoneal cavity. The abscess cavity should then be widely opened. Specimens should be sent for Gram stain and culture. Copious warm irrigation must be used at the end of the operation to properly cleanse the abdominal cavity. Closed-suction drains should be placed in dependent positions to reduce the risk of reaccumulation. In extremely contaminated cases, the incision may be left open and packed to prevent wound infection.

**ENTERIC FISTULAS**

**Definition and Etiology**

A *fistula* is defined as an abnormal communication between 2 epithelial surfaces. Enteric fistulas may arise in a number of settings: (1) diseased bowel extending to surrounding epithelialized structures; (2) extraintestinal disease eroding into otherwise normal bowel; (3) surgical trauma to normal bowel including inadvertent or missed enterotomies; or (4) anastomotic disruption following surgery for a variety of conditions. The first 2 generally occur spontaneously, while the latter 2 occur following surgical procedures. For the surgeon, the latter 2 are generally more problematic, in part because they are iatrogenic complications of surgery, but also because their early management often requires treatment of the critically ill patient with sepsis.

While this chapter overviews general considerations regarding the pathophysiology and management of enteric fistulas, it focuses on postsurgical enteric fistulas, particularly fistulas to the skin, that is, enterocutaneous fistulas. In this particular patient population, the mortality
rate remains high, between 3 and 22% in series dating back 6 decades, largely due to the frequent complications of sepsis and malnutrition (Table 16-5). Successful outcome requires a multidisciplinary team of health care workers, including surgeons, infectious disease specialists, intensivists, radiologists, nurses, enterostomal therapists, and nutrition specialists. Management of these patients must also take into account the psychosocial and emotional needs of the patient and his or her family through a prolonged and often complex treatment course.

One of the challenges in attempting to discern optimal management of these patients relates to the quality of the medical literature. Most reports are retrospective reviews of large case series emanating from referral institutions. Notwithstanding this shortcoming, these series provide general approaches to therapy, which help to guide treatment.

**Classification**

Fistulas involving the alimentary tract have traditionally been classified in 3 distinct ways: by the *etiology* responsible for their formation, that is, spontaneous versus postoperative; by the *anatomy* of the structures involved; and finally, by the *amount and composition of drainage from the fistula*. Such distinctions may provide important prognostic information about the physiologic impact of fistulas and the likelihood that they will close without

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**TABLE 16-5: COLLECTED SERIES OF OUTCOMES IN PATIENTS WITH OPERATIVE REPAIR OF ENTEROCUTANEOUS FISTULAS**

<table>
<thead>
<tr>
<th>Source</th>
<th>Period</th>
<th>Definitive Operation</th>
<th>Recurrence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soeers et al, 1979</td>
<td>1960-1970</td>
<td>76</td>
<td>13 (17)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Reber et al, 1978</td>
<td>1968-1977</td>
<td>108</td>
<td>22 (20)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>Soeers et al, 1979</td>
<td>1970-1975</td>
<td>88</td>
<td>19 (22)</td>
<td>18 (20)</td>
</tr>
<tr>
<td>Lynch et al, 2004</td>
<td>1994-2001</td>
<td>203</td>
<td>42 (21)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Draus et al, 2006</td>
<td>1997-2005</td>
<td>77</td>
<td>8 (11)</td>
<td>b</td>
</tr>
<tr>
<td>Visschers et al, 2008</td>
<td>1990-2005</td>
<td>107</td>
<td>10 (9)</td>
<td>13 (12)</td>
</tr>
</tbody>
</table>

*These deaths were “fistula related within 30 days of surgery.”

†The number of deaths in patients who were operated on could not be determined in this study.

surgical intervention.

**SPONTANEOUS VERSUS POSTOPERATIVE**

Enterocutaneous fistulas may be classified as either spontaneous or postoperative. Approximately three-quarters of fistulas occur in the postoperative setting, most commonly subsequent to procedures performed for malignancy, inflammatory bowel disease (IBD), or adhesive bowel obstruction. These fistulas become evident to the surgeon in a number of different ways: (1) They may occur in the early postoperative period as a septic complication of surgery, sometimes with catastrophic physiologic deterioration. This is usually a result of uncontrolled diffuse intra-abdominal infection caused by anastomotic leakage, breakdown of enterotomy closure, or a missed enterotomy. (2) They may occur in a more delayed manner, following treatment of a postsurgical infection with percutaneous drainage of a deep abscess or opening of a superficial wound infection that may reveal an underlying connection to the GI tract as a cause. (3) They may occur very late after the surgery due to unanticipated injury to the GI tract. The development of a wound infection following use of mesh for hernia repair would fall into this category either through erosion of mesh into bowel or due to iatrogenic injury to the bowel as one attempts to debride infected mesh.

Overly aggressive management of an open abdominal wound can also lead to intestinal injury and fistula formation, underscoring the importance of early definitive closure of the abdominal wall, preferably within the first 8 days from the original laparotomy. Fistulas have been reported to occur in up to 25% of patients during treatment with an open abdomen for abdominal sepsis. Two easily avoidable causes of fistulas in open abdomens managed with vacuum-assisted closure devices are feeding tubes inserted through the bowel wall during surgery and manipulation of anastomoses during VAC dressing changes.

The remaining 25% of fistulas occur spontaneously, that is, without an antecedent surgical intervention. These fistulas often develop in the setting of cancer or inflammatory conditions. Fistulas occurring in the setting of malignancy or irradiation are unlikely to close without operative intervention. Inflammatory conditions such as IBD, diverticular disease, perforated ulcer disease, or ischemic bowel can result in fistula development. Of these, fistulas in patients with IBD are most common; these fistulas may close
following a prolonged period of parenteral nutrition, only to reopen when enteral nutrition resumes.\(^37\)

**ANATOMIC CLASSIFICATION**

Fistulas may communicate with the skin (external fistulas: enterocutaneous or colocutaneous fistulas) or other intra-abdominal or intrathoracic organs (internal fistulas). Internal fistulas that bypass only short segments of bowel may not be symptomatic; however, internal fistulas of bowel that bypass significant length of bowel or that communicate with either the bladder or vagina typically cause symptoms and become clinically evident. Fistulas that occur in the absence of overlying soft tissue cover, known as enteroatmospheric fistulas, are among the most challenging types of fistulas. Identification of the anatomic site of origin of external fistulas may provide further information on the etiology and management of the fistula.

**Oral, Pharyngeal, and Esophageal Fistulas.** Radical resections and reconstructions for head and neck malignancy may be complicated by postoperative fistulas in 5% to 25% of cases.\(^38\) Alcohol and tobacco use, poor nutrition, and preoperative chemoradiation all contribute to poor wound healing and increase the risk of fistula formation. Failure of closure of the pharyngeal defect at the base of the tongue most commonly leads to fistula formation, and free microvascular flaps are the preferred method for closure. Brown and colleagues reported a significantly decreased postoperative fistula rate in patients who underwent free flap closure versus those with pedicled pectoralis flap closure, 4.5 versus 21%, respectively.\(^39\)

Most esophagocutaneous fistulas result from breakdown of the cervical anastomosis either following resection of esophageal malignancy or following esophageal trauma. Less common causes of oropharyngeocutaneous or esophagocutaneous fistula include tuberculosis, laryngeal or thoracic surgery, trauma, congenital neck cysts, anterior cervical spine fusion, and foreign body perforations.\(^40-42\)

**Gastric Fistulas.** The most commonly reported procedure associated with gastrocutaneous fistula formation is the removal of a gastrostomy feeding tube, particularly in children. The duration of gastrostomy tube placement appears to be related to the likelihood of development of a fistula after tube
removal, with nearly 90% of children developing a fistula when the tube had been in situ for more than 9 months.\textsuperscript{43} The rate of gastrocutaneous fistula following operations for nonmalignant processes such as ulcer disease, reflux disease, and obesity is between 0.5% and 3.9%.\textsuperscript{44} The recent rapid increase in the number of bariatric surgical procedures was anticipated to lead to an increase in the incidence of gastrocutaneous fistula following surgery for benign disease, as the rate of anastomotic leakage after gastric bypass surgery is 2% to 5%. One study has reported that approximately 10% of patients with staple line leaks go on to form chronic fistulas, making the overall rate less than 0.5%.\textsuperscript{45} Fistula formation following resection for gastric cancer remains a dreaded complication with significant mortality rates. Spontaneous gastrocutaneous fistulas are uncommon but can result from inflammation, ischemia, cancer, and radiation.

**Duodenal Fistulas.** The majority of duodenocutaneous fistulas develop after distal or total gastric resections or surgery involving the duodenum or pancreas. Inadvertent injury to or intentional excision of a portion of the duodenum during surgery of the colon, aorta, kidney, or biliary tract may also result in fistula formation. Spontaneous cases resulting from trauma, malignancy, Crohn disease, and ulcer disease account for the remaining duodenal fistulas.\textsuperscript{46,47} Prognostically, duodenal fistulas segregate into 2 groups: lateral duodenal fistulas and duodenal stump fistulas. Some authors have reported a decreased spontaneous closure rate with lateral duodenal fistulas when compared to that with duodenal stump fistulas.\textsuperscript{33,48}

**Small Bowel Fistulas.** Fistulas arising in the small bowel account for the majority of GI-cutaneous fistulas, the majority of which (70%-90%) occur in the postoperative period.\textsuperscript{37,49,50} Postoperative small bowel fistulas result from either disruption of anastomoses (either small bowel anastomoses or small bowel to colon anastomoses) or inadvertent and unrecognized injury to the bowel during dissection or closure of the abdomen. Operations for cancer, IBD, and adhesiolysis for bowel obstruction are the most common procedures antecedent to small bowel fistula formation. As noted previously, spontaneous small bowel fistulas arise from IBD, cancer, peptic ulcer disease, or pancreatitis.

Crohn disease is the most common cause of spontaneous small bowel fistula. The transmural inflammation underlying Crohn disease may lead to
adhesion of the small bowel to the abdominal wall or other abdominal structures. Microperforation may then cause abscess formation and erosion into adjacent structures or the skin. Approximately half of Crohn fistulas are internal and half are external. Crohn fistulas typically follow 1 of 2 courses. The first type represents fistulas that present in the early postoperative period following resection of a segment of diseased bowel. These fistulas arise in otherwise healthy bowel and follow a course similar to non-Crohn fistulas with a significant likelihood of spontaneous closure. The other group of Crohn fistulas arises in diseased bowel and has a low rate of spontaneous closure.

**Appendiceal Fistulas.** Fistulas of appendiceal origin may result from drainage of an appendiceal abscess or after appendectomy in a patient either without or with Crohn disease. In the latter case, the fistula often originates from the terminal ileum, not the cecum. The inflamed ileum adheres to the abdominal wall closure and subsequently results in fistula formation.

**Colonic Fistulas.** While spontaneous fistulas of the colon may result from inflammatory conditions such as diverticulitis, appendicitis, and IBD, or from advanced malignancy, the majority of colocutaneous fistulas are postsurgical, usually secondary to anastomotic breakdown following colonic resection for 1 of these conditions. Preoperative radiation therapy reduces the risk of local recurrence and death from advanced rectal cancer and is an accepted practice. However, radiation therapy contributes to both spontaneous and postoperative colocutaneous fistulas. Russell and Welch reported a 31% incidence of breakdown of primary anastomoses performed in irradiated tissues with resulting sepsis or fistula formation.

**Enteroatmospheric Fistulas.** Enteroatmospheric fistulas tend to occur within the first week of the open abdomen. The incidence of these fistulas depends on the baseline abdominal problem. In trauma patients managed with open abdomen, the incidence of enteroatmospheric fistulas varies between 2% and 25%. The incidence increases to more than 25% in open abdomens for intra-abdominal sepsis, and up to 50% in the setting of infected pancreatic necrosis.
PHYSIOLOGIC CLASSIFICATION

Traditionally, fistulas have been classified into high-output (>500 mL/d), moderate-output (200-500 mL/d), and low-output (<200 mL/d) groups. Enterocutaneous fistulas cause loss of fluid, minerals, trace elements, and protein, and, when improperly managed, they can result in profound irritation of the skin and subcutaneous tissues. Depending on the origin of the fistula and its anatomy, the amount of output and nature of the effluent may be estimated (Table 16-6). However, direct measurement of these parameters for an individual fistula allows for accurate replacement and an understanding of the physiologic and metabolic challenges to the patient. Classification of enterocutaneous fistulas by the volume of daily output provides information regarding mortality and has been used to predict spontaneous closure and patient outcome.33,58-60

<table>
<thead>
<tr>
<th>Source</th>
<th>Volume (mL/d)</th>
<th>pH</th>
<th>Na</th>
<th>K</th>
<th>HCO₃⁻</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>2000-2500</td>
<td>60</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>100</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1000</td>
<td>140</td>
<td>5</td>
<td>90-110</td>
<td>30-45</td>
<td></td>
</tr>
<tr>
<td>Bile</td>
<td>1500</td>
<td>140</td>
<td>5</td>
<td>35</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>3500</td>
<td>100-130</td>
<td>15</td>
<td>25-35</td>
<td>100-140</td>
<td></td>
</tr>
</tbody>
</table>

All values for sodium, potassium, bicarbonate, and chloride given in milliequivalents per liter.

In the classic series of Edmunds and associates, patients with high-output fistulas had a mortality rate of 54%, compared to a 16% mortality rate in the low-output group.33 More recently, Levy and colleagues reported a 50% mortality rate in patients with high-output fistulas, while those with low-output fistulas had a 26% mortality.58 Soeters and coworkers reported no association between fistula output and rate of spontaneous closure,37 while multivariate analysis by Campos and associates suggested that patients with low-output fistulas were 3 times more likely to achieve closure without operative intervention.60 The reason for these different closure rates most likely relates to the nature of the particular fistula, rather than the volume of output per se. If the fistula totally diverts flow, for example a pouting small bowel opening in the center of an open abdomen, it will be both high output
and unlikely to close, without these 2 factors being causally related. By contrast, a defect at a small bowel anastomotic site with a long fistula tract and no local infection will likely be walled off by surrounding tissues and close spontaneously. These fistulas, while initially high output, will often close because of favorable local conditions. In essence, prediction of closure should be based on the local conditions, and particularly the nature of the fistula rather than the output. To the extent that the output often reflects the nature of the fistula, it will then be predictive.

**Predicting Closure of Enterocutaneous Fistulas**

Spontaneous closure of enterocutaneous fistulas without the need for major surgical intervention is clearly a desirable outcome for these patients. The precise probability of spontaneous closure is somewhat difficult to assess since the large series reporting management of fistulas are usually derived from specialty centers for fistula management and thus not only represent a biased sample but also reflect differences in referral practice. Thus, spontaneous closure has been reported to occur in 10% to 80% of patients. Nevertheless, a number of factors have been suggested to be predictive of failure of spontaneous closure of fistulas (Table 16-7). Some of these factors are modifiable, for example, nutritional status, presence of local infection, and foreign bodies, while many are not, including location, proximal high output fistulas in the presence of an open wound, and the presence of distal obstruction. Knowledge of these factors should prove to be helpful in discussion of outcome with the patient and family members, as well as with the multidisciplinary team.

| TABLE 16-7: FACTORS THAT PREDICT FAILURE OF SPONTANEOUS FISTULA CLOSURE |
Distal obstruction
Local infection
Foreign body
Open abdomen
Epithelialized tract
Fistula characteristics:
  - Multiple fistula openings
  - Defect >1 cm
  - Short fistula tract
Abnormal bowel at origin of fistula (radiation, inflammatory bowel disease)
Profound malnutrition
High-output fistula
Jejunal origin of fistula


**Risk Factors and Prevention of Enterocutaneous Fistulas**

The majority of enterocutaneous fistulas arise in the postoperative period, often related to leakage of small bowel/colonic anastomoses or enterotomy closure. A number of factors have been associated with postsurgical enteric leaks. These can be divided into patient factors such as old age, immunosuppression, malnutrition, emergency surgery, and peritoneal contamination, and surgical factors such as emergency surgery, level of anastomosis, preoperative radiation, duration of surgery, blood loss, tension on anastomosis, inadequate blood supply to anastomosis, and technical error in suturing or stapling.

A recent study showed that diabetes was not a significant predictor of anastomotic leaks. However, diabetic patients who developed a leak had a mortality rate 4 times higher than nondiabetic patients. Moreover, preoperative steroids were associated with increased rates of anastomotic leaks in diabetics.66

Use of mechanical bowel preparation, anastomotic technique (stapled vs hand sewn; single vs double layer), and omentoplasty has not been shown to
influence anastomotic integrity. A meta-analysis in 2008 of 13 trials and 4601 patients showed no difference in the anastomotic leak rate when a mechanical bowel preparation was used compared to when it was not used in elective colon resection.\textsuperscript{57}

Clearly, optimization of modifiable factors will serve to reduce anastomotic leak. In the elective setting, operations may be delayed to allow for normalization of nutritional parameters, thus optimizing wound healing and immune function. In emergency operations, the luxury of optimizing nutritional status preoperatively is not possible. Instead, emphasis should be on adequate resuscitation and restoration of circulating volume, normalization of hemodynamics, and use of appropriate antibiotic therapy. Once a patient has been optimized preoperatively, attention is then turned to operative techniques to minimize the development of a fistula. Performance of anastomoses in healthy, well-perfused bowel without tension provides the best chance for healing. Testing of the rectal and sigmoid anastomoses with intraoperative air insufflations has been shown to reduce “radiologic” leak rate through guiding placement of additional sutures as needed.\textsuperscript{58} Careful hemostasis to avoid postoperative hematoma formation will decrease the risk of abscess, while inadvertent enterotomies and serosal injuries should be identified and repaired.

A recent meta-analysis based on 3 randomized trials showed that omentoplasty to buttress a colonic anastomosis did not reduce the rate of postoperative radiologic leaks, alter mortality, or change the need for reoperation.\textsuperscript{69} However, while omentoplasty per se does not reduce the probability of anastomotic leakage, interposition of an omental flap to separate the anastomosis from the abdominal incision may lessen the probability of injuring the bowel during closure or of an enterocutaneous fistula should anastomotic leakage occur.

A recent study pooling the data from 5 European randomized clinical trials studying rectal cancer care demonstrated that diverting stomas reduced the rate of symptomatic anastomotic leaks and improved overall survival but had no effect on cancer-specific survival.\textsuperscript{70} The differential survival was primarily attributable to early postoperative mortality. Proximal diverting colostomy or ileostomy may allow sufficient anastomotic healing prior to suture-line challenge by luminal contents.
Approach to Management

An organized treatment approach is of paramount importance to ensuring the optimal patient outcome. Table 16-4 lists overall mortality of patients presenting with enterocutaneous fistulas from a number of reports dating back 6 decades. Overall, the more recent studies appear to be associated with a lesser mortality rate, presumably a result of improvements in imaging, fluid resuscitation, antibiotic management, and intensive care support. However, the ultimate goals in treating patients with enterocutaneous fistulas are closure of the fistula with abdominal wall closure and return to baseline functioning level. Evenson and Fischer outlined 5 distinct phases of management that can be used to guide care of this patient population. These phases are discussed in detail and also summarized in Table 16-8.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Goals</th>
<th>Time Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognition/stabilization</td>
<td>Resuscitation with crystalloid, colloid, or blood</td>
<td>24-48 h</td>
</tr>
<tr>
<td></td>
<td>Control of sepsis with percutaneous or open drainage and antibiotics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electrolyte repletion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Provision of nutrition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control of fistula drainage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Commencement of local skin care and protection</td>
<td></td>
</tr>
<tr>
<td>Investigation</td>
<td>Fistulogram to define anatomy and characteristics of fistula</td>
<td>7-10 d</td>
</tr>
<tr>
<td></td>
<td>Other GI studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT scan to define pathology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Operative notes from prior surgery</td>
<td></td>
</tr>
<tr>
<td>Decision</td>
<td>Evaluate the likelihood of spontaneous closure</td>
<td>10 d-6 wk</td>
</tr>
<tr>
<td></td>
<td>Decide duration of trial of nonoperative management</td>
<td>When closure, unlikely or after 4-6 wk</td>
</tr>
<tr>
<td>Definitive management</td>
<td>Plan operative approach</td>
<td>Surgical intervention at 3-6 mo after patient stabilized</td>
</tr>
<tr>
<td></td>
<td>Refunctionalization of entire bowel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection of fistula with end-to-end anastomosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secure abdominal closure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastroscope and jejunostomy</td>
<td></td>
</tr>
<tr>
<td>Postsurgical</td>
<td>Usual postoperative protocol</td>
<td>Ensure access to ICU for management of potential complication</td>
</tr>
<tr>
<td></td>
<td>Psychological and emotional support</td>
<td>Team approach to management facilitates recovery</td>
</tr>
</tbody>
</table>

**TABLE 16-8: APPROACH TO MANAGEMENT OF ENTEROCUTANEOUS FISTULAS**

**PHASE 1: RECOGNITION AND STABILIZATION**

**Identification and Resuscitation.** As noted in the introduction, the clinical presentation of patients with enterocutaneous fistulas depends on the
underlying pathophysiologic process. Invariably, the patient who develops a postoperative enterocutaneous fistula will do well clinically for the first few days after operation. Within the first week, however, the patient may suffer delayed return of bowel function, as well as fever and leukocytosis, together suggestive of intra-abdominal infection. This setting will usually prompt a request for an abdominal CT scan that demonstrates a perianastomotic abscess. Percutaneous drainage for therapeutic management of the abscess will serve to confirm anastomotic disruption, either immediately or a few days later when there is evidence of enteric content. Occasionally, erythema of the wound develops and opening the wound reveals purulent drainage that is soon followed by enteric contents. In both of these circumstances, the peritoneal host defenses have successfully walled off and contained infection. By contrast, in some patients, diffuse peritoneal contamination arising from a leaking anastomosis or enterotomy causes profound and rapid deterioration of the patient with diffuse abdominal tenderness, evidence of organ dysfunction, and hemodynamic instability. Usually, these patients exhibit signs of organ dysfunction in the days prior to their catastrophic deterioration, including reduced level of consciousness, tachycardia, and mild renal impairment. The diagnosis then becomes clear, and management shifts from routine postoperative care to the management of a potentially critically ill patient. As with all critically ill patients, attention should turn to management of the ABCs.

The patient with a localized collection or one that has necessitated into the wound can usually be managed on the ward, while the patient with a more significant septic response may require transfer to an intensive care unit (ICU) setting. In both scenarios, restoration of intravascular volume, usually crystalloid, is appropriate with or without inotropic support as determined by physiologic monitoring. A Cochrane Database Systematic Review showed no difference in outcome in critically ill patients managed with crystalloid versus colloid and therefore recommended crystalloid as the preferable resuscitation fluid.72

The initiation of broad-spectrum antibiotic therapy should occur early and be directed toward the most likely pathogens involved. Patients with postoperative peritonitis have increased probability of having multiresistant microorganisms and should receive broader-spectrum antibiotics. The consensus guidelines published by the Surgical Infection Society/Infectious Diseases Society of America address antimicrobial options for these severe
health care–associated infections (see Tables 16-2 and 16-3).\textsuperscript{21}

**Control of Sepsis.** Uncontrolled infection with the development of a septic response and the concomitant fluid imbalance and malnutrition are the leading causes of mortality in modern series of enterocutaneous fistulas. The leakage of enteric contents outside of the bowel lumen may lead to a localized abscess or to generalized peritonitis. Percutaneous management of localized abscesses accompanied by appropriate antibiotic therapy and supportive measure is usually sufficient to resolve infection in this subgroup.

Diffuse peritoneal infection represents a much greater management challenge. In general, the generalized nature of the infection precludes successful therapy with percutaneous drainage, and therefore, an operative approach is indicated. Particularly in the early postoperative period, the surgeon should be wary of attempting to treat multiple intra-abdominal fluid collections observed on CT scan with percutaneous drains, when surgical intervention is required for definitive management.

**Surgical Approach.** The goals of operative management of peritonitis are to eliminate the source of contamination, reduce the bacterial inoculum, and prevent recurrent or persistent infection. The operative technique used to control contamination depends on the location and the nature of the pathologic condition in the GI tract.\textsuperscript{36}

For patients progressing to diffuse peritonitis in the early postoperative period, the abdomen is usually reentered through the previous incision with the discovery of pus and enteric content. One should refrain from making small incisions in those conditions, thereby avoiding inadequate exposure. After aspiration of the fluid, an exploration to find the source of contamination is warranted. Anastomotic dehiscence/enterotomy should generally be managed by exteriorization of the affected bowel. Whether this is performed via a single stoma site or with separate stomas (ie, end stoma plus mucous fistula) depends on the specific scenario. Obviously, if one is able to exteriorize the intestinal defect, the likelihood of a postoperative enteric fistula is markedly reduced. It is attractive to hope that a surgically repaired enterotomy or leaking enterotomy might heal primarily, given the obvious simplicity of the procedure. However, this is rarely successful in the setting of diffuse peritoneal infection, and therefore, this approach is not recommended. Reoperation after this misjudgment is fraught with potential
difficulty, in that the surgeon is faced with the need to reoperate on the patient in the early postoperative period. This laparotomy is invariably more difficult and is often associated with bleeding, further enterotomies, and a bowel that is extremely difficult to exteriorize. Under these circumstances, there should be consideration of a proximal defunctioning stoma if technically feasible. These cases are frequently the ones associated with inability to close the abdominal wall.

A number of anatomical circumstances may also preclude exteriorization of a leaking anastomosis. The principle of “defunction and drain” is appropriately applied in this setting. Most important among these is the rectal or sigmoid anastomosis where the distal end can be neither exteriorized nor closed. Unless the anastomosis is greater than 50% disrupted, it is reasonable to defunction with an ileostomy or a colostomy upstream and drain the site of the hookup. This approach is preferred as it increases the probability of future restoration of the GI tract. This is particularly true of leaks below the peritoneal reflection.\textsuperscript{73} If the anastomosis is almost completely disrupted, the surgeon is obliged to perform an end stoma and drain the pelvis, as the preserved anastomosis would stricture and preclude later stoma closure.

When a laparotomy is indicated for definitive source control in the presence of bleeding, massively damaged tissues, impeding physiologic exhaustion, and/or abdominal compartment syndrome, a damage control approach is advisable. This strategy, frequently used in trauma patients, consists of abbreviating the laparotomy in lieu of performing a definitive operation. The initial aim is to establish control of hemorrhage and/or intra-abdominal infection, followed by a period in the ICU for stabilization prior to definitive management. Total operative time should be less than 90 minutes during this phase.

A similar approach can be used in patients with leaking enterotomy, anastomotic dehiscence, and generalized peritonitis found during a laparotomy. In that setting, bowel resection with the stapled ends left inside the abdominal cavity in discontinuity and abdominal washout are performed followed by temporary abdominal closure. In subsequent operations, anastomoses are completed and the abdomen closed definitively. That approach was investigated in septic patients with generalized peritonitis due to a perforated diverticulitis Hinchey score of III/IV.\textsuperscript{74} In 9 of 15 patients, the local conditions and systemic state were considered adequate to perform primary anastomosis in the subsequent operation, hence avoiding a stoma.\textsuperscript{74}
Control of Fistula Drainage and Skin Care. Concurrent with drainage of sepsis, a plan to control fistula drainage and provide local skin care will prevent continued irritation of the surrounding skin and abdominal wall structures. Obviously, fistulas created following percutaneous drainage of abscesses are usually well managed by the drain itself. Indeed, the drainage of a local infection is frequently sufficient to permit closure of the fistula. For small low-output fistulas, dry dressing may suffice. In less controlled circumstances, particularly in the setting of the open abdomen, control of the effluent is not straightforward and must be managed aggressively.

There are several resourceful techniques to manage a GI fistula in the setting of an open abdomen. The main goal in all of them is to isolate fistulous drainage from the open wound and the abdominal cavity, thereby obtaining adequate source control and preventing peritonitis. Those goals can be achieved with or without concomitant vacuum-assisted wound therapy techniques.

The method known as “floating stoma” consists of adapting an ostomy bag to an opening created on a plastic silo sutured to the abdominal wall. This method does not use vacuum therapy and is the basis for the other techniques. At least 4 other methods use vacuum-assisted wound management in association with control of bowel effluent through the adaptation of different types of catheters/bags to the fistulous opening. A skilled enterostomal therapist can often provide useful insight into these issues and should work in concert with a dedicated nursing team.

The goals of therapy are to protect the skin, accurately monitor output, and minimize patient anxiety over effluent control. Use of a drainable pouching system that is tailored to the size of the open wound is effective. This is often combined with other ostomy-based accessories such as hydrocolloid sheets and paste to protect perifistular skin and to provide a base on which to secure the pouching system (Figs 16-2 to 16-5).
FIGURE 16-2 Small bowel enterocutaneous fistula adjacent to an ileostomy with significant skin and subcutaneous tissue breakdown. Top arrow: fistula. Bottom arrow: ileostomy. (Used with permission from Jo Hoeflok, Nurse Practitioner/Enterostomal Therapy Nurse, St. Michael’s Hospital, Toronto.)
FIGURE 16-3 The skin around of the wound is covered with an overlapping protective barrier (hydrocolloid sheets), and stoma paste is applied to the borders to prevent undermining of gastrointestinal contents. (Used with permission from Jo Hoeflok, Nurse Practitioner/Enterostomal Therapy Nurse, St. Michael’s Hospital, Toronto.)
FIGURE 16-4 The entire wound and the protective barrier are covered with a thin plastic film. A pouch with stoma paste is attached to an opening on the plastic film. [Used with permission from Jo Hoeflok, Nurse Practitioner/Enterostomal Therapy Nurse, St. Michael’s Hospital, Toronto.]
Vacuum-assisted closure devices have been reported to aid in the care of these complicated wounds, including the promotion of closure. For example, Wainstein and coauthors reported promising results after reviewing their 10-
year experience with vacuum-assisted closure devices. In this study, fistula output was profoundly suppressed soon after commencing use of the device, and spontaneous closure was achieved in 46% of patients. The use of a vacuum-assisted device was also found to reduce the frequency of wound dressing changes and improve dermatitis in all cases. These findings are consistent with most surgeons’ anecdotal experience with vacuum treatment.

Some authors have reported a small number of patients developing new enteric fistulas with the vacuum device. Therefore, it is of utmost importance that a sheet of nonadhesive material is placed on top of the exposed viscera and beneath the peritoneum of the abdominal wall prior to any vacuum device in the open abdomen. It is also important to emphasize that when using vacuum-assisted wound therapy in the presence of GI fistula, the negative pressure should only be applied to the open abdomen surrounding the fistula. Otherwise, it will damage the fistulized bowel. Presumably, stable patients with some granulation overlying the exposed bowel have lower risk of fistulas.

Reduction in Fistula Output. While fistula output does not correlate with the rate of spontaneous closure, reduction in fistula drainage may facilitate wound management and decrease the time to closure. Further, reduced output enhances the ease of fluid and electrolyte management and may make local wound care easier. In the absence of obstruction, prolonged nasogastric drainage is not indicated and may even contribute to morbidity in the form of patient discomfort, impaired pulmonary toilet, alar necrosis, sinusitis or otitis media, and late esophageal stricture. Measures to decrease the volume of enteric secretions include administration of histamine antagonists or proton pump inhibitors. Reduction in acid secretion will also aid in the prevention of gastric and duodenal ulceration as well as decrease the stimulation of pancreatic secretion. Antimotility agents such as loperamide and codeine may also be effective.

As inhibitors of the secretion of many GI hormones, somatostatin and octreotide were postulated to promote nonoperative closure of enterocutaneous fistulas. This had been challenged in the past. However, a meta-analysis found that a significant number of fistulas did in fact close with somatostatin and somatostatin analogues when compared to a control group. In addition, the time to closure was also significantly faster. Another systematic review and meta-analysis of 720 studies found similar results with
regard to the time to closure when compared to a placebo, with a weighted mean difference of 6.37 days. Hospital stay was also significantly decreased, but no mortality difference was observed.\(^{83}\) Infliximab, a monoclonal antibody to TNF-\(\alpha\), has been shown to be beneficial in inflammatory and fistulizing IBD.\(^{84}\) In a randomized trial of patients with chronic fistulas (duration >3 months), administration of infliximab resulted in a significantly increased rate of closure of all fistulas when compared to placebo.\(^{84}\) Some evidence suggests a role for infliximab in treatment of fistulas complicating IBD, and its use has been reported to promote healing of persistent fistulae even in non-IBD patients.\(^{85}\)

A number of other approaches to managing fistula output and promoting closure have been reported. These include endoscopic injection of fibrin glue into identified fistula openings,\(^ {86}\) radiologically guided percutaneous Gelfoam embolization of the enteric opening, and the insertion of an absorbable fistula plug using a combination of percutaneous and endoscopic approaches.\(^ {87}, {88}\) All 3 involve the “plugging” of the opening with a biological material, presumably with the expectation of tipping the local conditions toward healing. A study of 145 patients aimed at determining the efficacy and safety of autologous, platelet-rich fibrin glue (PRFG) found that time to closure was shorter (7 vs 23 days) and likelihood of closure within the first 28 days (77% vs 57%) and overall closure was greater with PRFG.\(^ {89}\) These low-morbidity techniques may therefore be considered as adjuvant considerations for fistula management. One would speculate that their greatest efficacy would be in the setting of a long tract, without epithelialization and with low output. Endoscopic insertion of a silicone-covered stent across the fistula opening related to gastrojejunal leak following gastric bypass surgery has been described as a means of allowing early feeding and promoting fistula closure.\(^ {45}\) One well-documented and potentially morbid complication of the stent use is its downstream migration with obstruction and erosion of the intestine. Clearly, no consensus regarding use of this approach has been achieved, given the small patient numbers described.

**Nutritional Support.** Malnutrition may be present in 55% to 90% of patients with enterocutaneous fistulas.\(^ {37}\) Even though provision of nutritional support and time may be all that are necessary for spontaneous healing of
enterocutaneous fistulas, normalization of nutritional parameters will optimize patients requiring a surgical intervention. However, malnutrition is a major contributor to mortality in that setting. Patients with postoperative enterocutaneous fistulas are often malnourished due to a combination of poor enteral intake, the hypercatabolic septic state, and the loss of protein-rich enteral contents through the fistula and via the open abdominal wall.

The optimal route of nutrition in the management of enterocutaneous fistulas has not been critically studied. Parenteral nutrition has long been the cornerstone of support for patients with enterocutaneous fistulas. This, in part, is related to the fear that early enteral feeds will exacerbate the fistula through increasing output and also that enteral feeds may not be an adequate form of nutritional support. Parenteral nutrition can be commenced once sepsis has been controlled and appropriate intravenous access has been established. Transition to partial or total enteral nutrition has been advocated in recent reports to prevent atrophy of GI mucosa as well as support the immunologic and hormonal functions of the gut and liver. In addition, parenteral nutrition is expensive and requires dedicated nursing care to prevent undue morbidity and mortality from line insertion, catheter sepsis, and metabolic complications. Thus, attempting enteral feeding is appropriate in most fistula patients. As achieving goal rates of enteral feeding may take several days, patients are often maintained on parenteral nutrition as tube feedings are advanced. Enteral feeding may occur per os or via feeding tubes placed nasogastrically or nasoenterically. Enteral support typically requires 4 ft of small intestine and is contraindicated in the presence of distal obstruction. Drainage from the fistula may be expected to increase with the commencement of enteral feeding, although this does not uniformly occur and is often dependent on fistula location and size of the fistula defect; however, spontaneous closure may still occur, often preceded by a decrease in fistula output. When parenteral and enteral nutrition are both options, the latter is preferred. It is far less expensive, safer, and is easier to administer (particularly if the intent is to manage the patient as an outpatient). A meta-analysis by Gramlich and colleagues indicated that ICU patients receiving enteral feeds have a lesser infection rate than those receiving parenteral feeds.

In patients with high-output proximal fistulas, it has been suggested to provide enteral nutrition by a technique called fistuloclysis. In fistuloclysis, an enteral feeding tube is placed directly into the matured high-output fistula. Teubner and colleagues reported on their experience using
fistuloclysis in 12 patients before reconstructive surgery.\textsuperscript{94} Eleven of 12 patients were able to discontinue parenteral support, and nutritional status was maintained until surgery in 9 patients (19-422 days) and for at least 9 months in the 2 patients who did not undergo operative intervention.\textsuperscript{94} Of note, surgeons in this study also reported improved bowel caliber, thickness, and ability to hold sutures in patients who had received enteral nutrition.\textsuperscript{94} Other measures such as the use of recombinant human growth hormone on fistula patients have been examined. While able to promote intestinal mucosal epithelial cell proliferation; increase levels of total proteins, albumin, fibronectin, and prealbumin; and transfer and reduce nitrogen excretion, its clinical role has not been clearly defined.\textsuperscript{95}

**Psychological Support.** Patients who develop postoperative enterocutaneous fistulas require considerable psychological support. They have sustained a major complication of surgery and are frequently faced with prolonged postoperative stay, excessive abdominal discomfort, and potentially 1 or more additional surgical interventions. In aggregate, all of these factors lead to psychological distress for patient and their families and should be addressed once the acute disease is dealt with.

**PHASE 2: INVESTIGATION**

Once the patient has been stabilized with control of sepsis and commencement of nutritional support, early radiologic investigation may be of value. Abdominal CT scanning with GI contrast will help to discern whether there is residual local infection that requires drainage, will localize the level of the fistula and the amount of contrast flowing beyond the defect, and occasionally will indicate whether there is distal obstruction. Fistulograms down drainage tracts will elucidate the length, course, and relationships of the fistula tract. If the fistula is spontaneous, the nature of the local pathologic process from which the fistula arises may be determined. In the setting where the mucosal bud of the fistula is readily observed in the center of an open abdomen, aside from a CT scan to rule out distant infection, little further early imaging is required. Because patients with enterocutaneous fistulas are frequently referred to larger centers for management, it is essential that all notes, particularly operative notes, be obtained from the referring hospital. Personal communication with the surgeon may further
elucidate other factors in the patient’s disease that are not readily evident from the notes.

**PHASE 3: DECISION**

Spontaneous closure of fistulas restores intestinal continuity and allows resumption of oral nutrition. As noted previously, the rate of spontaneous closure varies considerably from series to series, with an average of approximately one-third of patients. This wide range likely represents patient selection in the various series, and in particular, whether the series emanates from a referral center where the patient population tends to be more complex. A number of factors predict spontaneous closure. These are listed in Table 16-7. One might consider 2 case scenarios to illustrate these points. A long, narrow fistula tract originating from a small leak in a colonic anastomosis with no evidence of distal obstruction and a well-drained perianastomotic abscess is almost certain to close spontaneously. By contrast, a small bowel defect revealing itself as a mucosal bud in the middle of an open abdomen is unlikely to heal as the tract is short and epithelialized, in essence mimicking a stoma.

Fistulas associated with IBD often close with nonoperative management only to reopen upon resumption of enteral nutrition. These fistulas should be formally resected once closed to prevent recurrence. Fistulas in the setting of malignancy or irradiated bowel are particularly resistant to closure and would suggest the need for earlier operative intervention.

Most authors agree that once resuscitation, wound care, and nutritional support are established, 90% to 95% of fistulas that will spontaneously close typically do so within 4 to 8 weeks of the original operation. In the absence of closure, there should be consideration of surgical closure. Like any surgical procedure, weighing of the risk and benefits of surgical intervention is critical prior to proceeding to operation. This is particularly relevant in this patient population where the surgical procedure is a major one and has a finite risk of recurrence. Some patients are perfectly well, tolerating a regular diet, and have fistula effluent that is trivial in volume and requires only coverage with dry gauze. The potential risks of a major operation in this type of patient might outweigh the ultimate benefit.

The timing of elective operative intervention for fistulas that are unlikely to or fail to close is extremely important. Early operation is only indicated to
control sepsis not amenable to percutaneous intervention. These early procedures are typically limited to drainage of infected fluid collections and defunctioning or exteriorization of the defect.

There is some controversy in the literature as to how long one should wait before attempting definitive elective closure of enterocutaneous fistulae. Very early closure appears to be contraindicated because the patient condition is generally not optimized. Further, from a technical standpoint, adhesions tend to be dense and vascular, therefore rendering the procedure difficult. In one retrospective study, Keck and colleagues observed that operative difficulty and denser adhesions leading to inadvertent enteromies were more common when patients were taken to surgery for reversal of a Hartmann procedure before 15 weeks compared to after. Poor outcome when surgery is performed in the 2-week to 3-month window has been report by several groups. At least 2 reports suggest that a very long delay before definitive surgery (>36 weeks) might adversely affect outcome. It is generally recommended that definitive surgery be considered in the window of 3 to 6 months after the patient is stabilized from the initial recovery from the procedure that led to the fistula formation. Various factors will influence where, in this interval, surgery is performed. Patient factors such as nutritional status, ease of managing the fistula, and family support may influence decision making. Some authors talk about the “soft” abdomen and prolapse of the fistula as being valuable clinical signs that peritoneal conditions are reasonable to proceed with surgery. On occasion, there is intense pressure from the patient and family to reoperate and “fix” the fistula during this early period. This approach should be resisted.

**PHASE 4: DEFINITIVE MANAGEMENT**

Operations repairing enterocutaneous fistulas may be complex and often lengthy. In addition to repairing the fistula, many of these patients require complex abdominal wall closures. Before definitive management, the patient should have achieved optimal nutritional parameters and be free of all signs of sepsis. Through careful management of fistula drainage, a well-healed abdominal wall without inflammation should be present. Given the complexity of these operations and importance of perioperative multidisciplinary care, surgical management in certain countries is dedicated to regional centers. For example, in the United Kingdom, 2 supraregional
centers are nationally designated. Having said that, Murphy and colleagues did demonstrate that surgical outcomes in regional units closer to home might be as successful with an appropriate dedicated multidisciplinary team.102

Consent. As for all operations, the patient should be fully apprised of the nature of the procedure and its potential for complications. Connolly and colleagues reported a very high incidence of complications following intestinal reconstructive surgery (82.5% of procedures) when one considered postoperative nosocomial infections including surgical site infections, respiratory infections, and central line sepsis together with postsurgical myocardial dysfunction, GI bleeding, and deep vein thrombosis.103 In one of the larger studies by Owen and colleagues, 153 patients underwent definitive operative intervention for enterocutaneous fistulas. Of these, 88% were small bowel in origin and 52% of were high output. Successful closure occurred in 83% of patients; however, like previous reports, postoperative complications were high, occurring in 87% of patients, with a 30-day mortality of 3.9% and 1-year mortality of 15%.104

In discussions with patients and their families, the unique difficulty of these procedures should be raised, pointing out the potential for adhesions and therefore inadvertent injury and excessive bleeding. The fistula recurrence rate is also significant, with reported rates up to 33% (see Table 16-5), depending on the individual circumstance. The patient and relevant family members should know that the procedure may be prolonged and may require an ICU stay in the postoperative period. Some of the anxiety of the patient may be related to mistrust of physicians in general following a previously complicated operation. Clearly, the sensitive nature of reoperation for prior complications requires a strong physician-patient relationship to minimize patient anxiety prior to the planned procedure.

Patient Preparation. It is critically important for the operating surgeon to fully understand the nature of the patient’s prior surgeries. Reviewing the previous operative notes as well as speaking with the original surgeon will consolidate one’s knowledge of the initial pathologic process and the precise anatomy to be corrected in the reoperative setting. One should also be very liberal about using preoperative contrast imaging or endoscopy to completely define the anatomy. In the hypothetical case of reoperation after a colonic anastomotic dehiscence, the need for definition of the anatomy varies
according to the initial source control procedure. It is of utmost importance to confirm distal patency of the gut before any operation. In preparation for closure of a Hartmann procedure, the rectal stump should be routinely investigated by endoscopy. This may help with planning of the operation as well as locating the stump at surgery. Closure of a defunctioning ileostomy or colostomy should also be preceded by investigation of the downstream anastomosis. This is intended to rule out the presence of a stricture or persistent defect at that site, both of which would alter surgical approach. Finally, contrast studies are essential when complex fistulas exist and are to be treated by reoperative surgery.

The general principles related to preparation for any surgery should be applied to reoperation. These would include optimization of the general medical status of the patient, administration of subcutaneous heparin and/or other antithrombotic strategies, and initiation of measures aimed at reducing postoperative infectious complications. Orthograde intestinal lavage by mouth as well as distally via the defunctioned limb has been recommended for mechanical preparation of the bowel. However, the evidence underlying this recommendation is limited, and, in fact, studies show that mechanical bowel preparation for elective colon surgery does not improve outcome and may have some deleterious effects. Our practice is to forego the use of mechanical prep unless reconstruction involves passage of stapling device transanally. Clearance of inspissated mucus in the rectal stump with an enema may facilitate advancement of the stapler proximally. Finally, prophylactic intravenous antibiotics with broad-spectrum coverage of both facultative gram-negative and anaerobic bacteria are indicated. Consideration of coverage of resistant microbes should be made.

**Operative Intervention.** Patients should be positioned to permit optimal exposure to the field of surgery, to take into account potential requirements for extension of the operative field, and to facilitate optimal reconstruction of the GI tract and/or drainage of the operative field. In the majority of situations, the supine position is adequate. Concomitant lithotomy positioning is often helpful, particularly when reconstruction involves the left colon or rectum, where transanal access for endoscopy or stapling may be useful. When reoperation involves the upper GI tract, left lateral decubitus positioning will allow an initial thoracoabdominal incision or extension of an abdominal incision into the chest.
Careful planning of the location and type of incision are mandatory prior to making the initial incision. It is preferable to enter the peritoneal cavity through a previously unoperated area of the abdominal wall, thereby avoiding the areas where the most intense adhesions would be expected, that is, beneath the previous abdominal wall incision and in the region of the abdomen where the inflammation might have been the most severe. Inadvertent enterotomy is relatively common during reoperation, occurring in approximately 20% of patients, and is associated with a higher rate of postoperative complication and a longer postoperative hospital stay. In addition, it is a frustrating beginning to an often long and tedious operation.

The use of the midline incision, beginning with entry either cephalad or caudad to this initial incision through an unoperated field, is the most common approach to reentering the abdomen. This approach provides broad access to the peritoneal cavity with opportunity for extension and is also readily closed. Other approaches may include unilateral or bilateral subcostal incisions, transverse incisions, flank incisions, or thoracoabdominal incisions. In general, these should be considered when a specific area of the abdomen is operated on, because they generally afford less access to the overall peritoneal cavity. When placing new incisions, care should be taken not to render intervening tissue bridges ischemic. This might occur when a midline incision is placed adjacent to a previous paramedian incision. It is preferable to use the previous paramedian incision with extension into the midline above or below. When the fistula opening is in the center of a reepithelialized section of the abdomen with no underlying fascia/muscle, one should preferably enter the abdomen as described above, either cephalad or caudad to the previously operated area. When this is not possible, one should consider placing the initial incision along the line of the fascial edge, rather than though the reepithelialized portion. In the latter operative field, the skin may be very adherent to the underlying bowel, therefore increasing the chance of bowel injury. This is particularly true when there is retained mesh, which may have contributed to fistula formation in the first place.

Upon entering the peritoneal cavity, adhesions between the anterior abdominal wall and the underlying omentum and bowel must be released. By 3 to 6 months following the initial surgery, adhesions are generally relatively filmy and readily divided using scissor or cautery dissection. Gentle traction on the bowel with countertraction on the abdominal wall will facilitate exposure of the appropriate tissue plane for division. A similar approach is
appropriate for dense adhesions, with some surgeons preferring knife dissection. During this dissection, it may be necessary to leave patches of abdominal wall (peritoneum with or without fascia) or even mesh adherent to bowel to avoid enterotomy. It is also noteworthy that enterotomies may be caused by traction on the bowel due to retraction on the abdominal wall. Clearance of the fascial edges along both sides of the entire incision is necessary to achieve adequate and safe closure of the abdominal wall.

Having successfully entered the abdominal cavity, one faces varying degrees of interloop adhesions. The degree to which these must be lysed depends on the particular operation to be performed. When one is operating on the colon for the purpose of stoma closure or reestablishment of colonic continuity, there is generally little need to exhaustively take down small bowel adhesions. The fact that the patient has been tolerating a normal diet preoperatively provides ample evidence that the small bowel adhesions are not of physiologic significance. However, care should be taken not to twist the gut when placing it in the abdominal cavity through small incisions. While not having to lyse all adhesions, it is necessary, however, to free small bowel loops from their attachments to the colon so that the latter might be adequately mobilized to permit easy closure or anastomosis.

On the other hand, when operating to close a small bowel stoma or to correct an enterocutaneous fistula, one should consider more comprehensive lysis of adhesions along the entire length of the small bowel, specially the distal small bowel. This approach is particularly important in the setting of a previous open abdomen with granulation tissue or reepithelialization of the abdominal wall. The presence of a stoma or fistula may serve to defunction a distal small bowel adhesive obstruction prior to surgery and may therefore preclude its recognition. The presence of a distal obstruction following upstream anastomosis could prove catastrophic in the postoperative period. Therefore, one should always confirm patency of the distal bowel before performing an anastomosis.

Adhesiolysis varies considerably in its degree of difficulty. Even when the reoperation is appropriately delayed from the initial operative procedure and vascularized adhesions are no longer present, the number and density of residual fibrous adhesions may still be significant and represent a significant technical challenge. As described for opening the peritoneal cavity, good lighting of the operative field, excellent surgical assistance, and a dose of patience are absolute requirements for this part of the operation. Two
experienced surgeons working together facilitate adhesiolysis. During lysis of adhesions, one should also be wary of encountering previous anastomoses. Adhesions may be particularly tenacious in these areas, particularly when the prior anastomosis was performed using a stapled technique. For side-to-side functional end-to-end stapled anastomoses, the crotch of the anastomosis may be mistaken for intense adhesions. Failure to recognize this may result in inadvertent enterotomy and the attendant increased morbidity.

When surgery has been timed appropriately, one usually finds the dissection distant from the fistula to be reasonably straightforward. As one approaches the fistula site, it becomes increasingly tedious with multiple adherent loops of bowel. We recommend that the fistula be addressed relatively late in the dissection, after most of the small bowel has been mobilized. This minimizes inadvertent injury to loops of bowel uninvolved in the fistula.

Several of the large case reviews address surgical technique and risk of recurrence. In general, it appears to be preferable to locally resect the segment of small bowel bearing the fistula rather than simply closing the intestinal opening. The latter approach frequently fails. In the case of impossibly dense adhesions precluding mobilization and resection, one might consider the addition of a temporary proximal defunctioning stoma.

In the elective surgical setting, stapled anastomoses have been shown to be equivalent to hand-sewn anastomoses in terms of anastomotic dehiscence. By contrast, in trauma patients, comparative and case-control studies (level of evidence 3) showed that hand-sewn anastomosis of the small bowel had fewer leaks and fewer intra-abdominal abscesses than stapled technique. However, that finding was not reproduced in large bowel anastomosis in the same setting. With respect to closure of enterocutaneous fistulas, hand-sewn appears to be the preferred approach to performing the anastomosis following resection. Whether 1 layer versus 2 layers of sutures or running versus interrupted stitching should be used has not been systematically addressed. Frequently, the chronically defunctioned bowel is atrophic, line-walled, and stiff. Under these circumstances, the stapling devices are unable to accommodate the pathologic nature of this bowel, where hand-sewing can better accommodate differences in size, thickness, and compliance of the intestine.

Wrapping of the anastomosis with omentum has been examined as a
means of preventing anastomotic leakage but has not proven to be effective.\textsuperscript{70} However, placement of a flap of omentum between the fresh anastomosis and the abdominal wall closure may minimize recurrence of fistulization. Some have advocated the placement of a decompressive gastrostomy and/or the placement of a feeding jejunostomy, both of which may aid in the postoperative care of patients undergoing procedures of this scale.

As the cumulative experience with complex laparoscopic procedures has increased, several groups have reported laparoscopic approaches to enteric and enterocutaneous fistulas.\textsuperscript{109-114} The largest of these series reported 73 procedures in 72 patients, 20\% of which were enterocutaneous fistulas.\textsuperscript{113} The authors reported a mean operative time of 199 minutes with a 4.1\% conversion rate.\textsuperscript{113} Because surgical procedures for the management of enteric fistulas are generally complex ones, a laparoscopic approach would seem appropriate only in the hands of a skilled and experienced laparoscopic surgeon and only in selected circumstances.

**Abdominal Wall Closure.** Results of a recently published systematic review and meta-analysis involving patients with open abdomens showed that the average primary fascial closure rate was 62\%.\textsuperscript{115} Therefore, after the fistula has been appropriately managed, one is left with the challenge of closing the abdominal wall. The complexity of this aspect of the operation varies depending on the preoperative state of the abdominal wall. Closure may be straightforward when the enterocutaneous fistula is along a previous drain tract or through necessitation of an abscess through an abdominal wound. By contrast, when the prior patient management involved an open abdomen approach with the fistula draining from the center of the wound, patients may present with large ventral hernias that are not amenable to simple fascial closure. In advance of surgery, it is essential that the surgeon consider management of the abdominal wall a significant part of the procedure and reflect upon the various surgical options. Included in these preoperative deliberations should be the proactive involvement of a plastic surgeon to aid in the assessment of options and to potentially prepare him or her for involvement in the operation. Table 16-9 outlines the various approaches. Prior to beginning abdominal wall closure, it is desirable to debride/remove any residual infected foci, including chronically infected suture material and previously placed infected mesh. One should also attempt to position the intestinal anastomosis away from the closure and, if possible, to interpose
omentum between the anastomosis and the abdominal wall. Finally, it is generally considered that, in the setting of GI surgery where there is contamination of the surgical field, the use of nonabsorbable permanent mesh is contraindicated as it is associated with an increased risk of infection and fistulization.\textsuperscript{116}

**TABLE 16-9: MANAGEMENT OF ABDOMINAL WALL FOLLOWING ELECTIVE CLOSURE OF GASTROINTESTINAL FISTULA**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Preoperative Fascial Defect</td>
<td>- Primary closure with or without some fascial relaxation</td>
</tr>
<tr>
<td>Preoperative Fascial Defect</td>
<td>- Small defect (&lt;5 cm)</td>
</tr>
<tr>
<td></td>
<td>- Primary fascial closure with or without some fascial relaxation</td>
</tr>
<tr>
<td></td>
<td>- Large defect</td>
</tr>
<tr>
<td></td>
<td>- Primary fascial closure using component separation technique</td>
</tr>
<tr>
<td></td>
<td>- If very large, may be combined with prosthetic material</td>
</tr>
<tr>
<td></td>
<td>- Coverage with vascularized flap</td>
</tr>
<tr>
<td></td>
<td>- Use of prosthetic material</td>
</tr>
<tr>
<td></td>
<td>- Nonabsorbable</td>
</tr>
<tr>
<td></td>
<td>- Absorbable</td>
</tr>
<tr>
<td></td>
<td>- Nonbiological</td>
</tr>
<tr>
<td></td>
<td>- Biological</td>
</tr>
</tbody>
</table>

When no defect or a small defect in the fascia exists, primary closure is usually achievable. However, if primary closure is not achieved within the first 7 to 10 days, patients will likely require additional procedures to bridge the gap in the abdominal wall, since closure under tension can result in abdominal compartment syndrome, evisceration, and/or incisional hernias. In these circumstances, relaxing incisions placed in the aponeurosis of the external oblique muscle approximately 2 cm lateral to the edge of the rectus muscle may minimize any tension. Polydioxanone, a slowly absorbable monofilament suture material, appears preferable as it is equivalent to nonabsorbable monofilament suture in terms of recurrent hernias but has less wound pain and sinus formation.\textsuperscript{117}

Various closure techniques have been proposed when primary fascial
There has been increasing enthusiasm regarding the use of the component separation technique as a means of achieving abdominal wall closure without prosthetic material. In brief, this approach involves the separation of the external oblique and internal oblique muscles bilaterally plus division of the posterior rectus fascia. Together, these accomplish up to 12-, 22-, and 10-cm advancements of the upper, middle, and lower thirds of the abdomen, respectively. This approach has been reported for abdominal wall closure after trauma surgery, in patients with sepsis managed with the open abdomen, and in patients with enterocutaneous fistulas. Wind and colleagues examined the application of this technique in the presence of a contaminated abdominal wall defect, including during closure of an enterocutaneous fistula and/or stoma. This study reported the feasibility of this approach in terms of achieving abdominal wall closure but noted considerable morbidity, including wound seromas, wound infections, and hematomas as well as recurrent abdominal wall hernias in approximately 22% of patients. Recurrence of the enterocutaneous fistula occurred in 25% of patients. In a small percentage of patients, the use of absorbable mesh was combined with the component separation technique, because the advancement of the abdominal wall alone was not sufficient to cover the defect.

A new technique devised by our group incorporates 2 longitudinal incisions in the anterior and the posterior rectus sheaths, followed by abdominal wall reconstruction using 2 large synthetic meshes with antiadhesive coatings facing the abdominal cavity. This method creates 3 overlapping layers over the abdominal cavity and allows medialization of the rectus abdominis muscles as described by Lázaro da Silva. Twelve patients with open abdomens underwent the procedure thus far; definitive closure was achieved in all cases. A follow-up at 36 months showed no incisional hernias or fistulas.

Finally, absorbable prosthetics may be considered for management of the defect in a multistage reconstructive approach. Synthetic meshes such as polyglactin effect good initial coverage but have the anticipated long-term consequence of incisional hernia formation. As an alternative, single-stage reconstruction with biological prostheses including porcine collagen mesh and acellular dermal matrix have been suggested with the potential advantage of increased resistance to infection. A recent study showed that despite
unquestionably lower complication rates with biological prosthesis compared to other materials, there was a 50% incidence of recurrent ventral hernia in the setting of infection within the first 3 years. Moreover, the presence of enterocutaneous fistulas has also been linked to unfavorable outcomes.

In summary, management of the abdominal wall following reoperative surgery in these patients may be a considerable challenge. The major objective is to prevent recurrent fistula formation and minimize postoperative infection. Prevention of late ventral hernia formation is a secondary goal. Involvement of a surgical team with expertise in the options, including the use of the component separation technique, would appear to broaden the clinical options for the patient.

**PHASE 5: POSTSURGICAL PHASE**

The postoperative period can be divided into 2 parts: the early postsurgical recovery period and the later rehabilitation and convalescence phase. The former of these periods can be somewhat complex as postoperative complications are frequent, with up to 80% of patients having 1 or more complications. In particular, these patients have a significant incidence of postoperative infection, both at the surgical site and at distant sites including lung and central venous lines. As shown in Table 16-5, the incidence of recurrent fistulization following surgery is considerable and is associated with prolonged hospital stays and repeat admissions to the ICU as well as repeat interventions. Brenner and colleagues reported that recurrence of the enterocutaneous fistula in the postoperative period was the strongest predictor of mortality, invariably due to the development of overwhelming sepsis and organ failure. Mortality is related to the presence of preoperative comorbidities. Short of death, the recurrence of enterocutaneous fistula following surgery represents a major complication. Among those who survive this recurrence, only 50% to 66% go on to further surgery and successful closure, while the remainder live with a chronic fistula. A number of factors predict recurrence (Table 16-10).

| TABLE 16-10: FACTORS PREDICTING RECURRENCE AFTER ELECTIVE REPAIR OF ENTEROCUTANEous FISTULA |
Patient Factors
Open abdomen
Origin of fistula (small bowel > large bowel)
Underlying inflammatory bowel disease
“Frozen abdomen” or residual intra-abdominal infection

Surgical Factors
Timing of surgery (<4 weeks, >36 weeks)
Multiple inadvertent enterotomies at reoperation
Oversewing of enteric defect, rather than resection and anastomosis
Use of stapled anastomosis, compared to hand-sewn anastomosis
Need to perform mesh closure of abdominal wall

By the time their fistulas have been surgically closed, these patients have often been undergoing medical care, usually both as inpatients and outpatients, for several months following the initial development of their enterocutaneous fistulas. By the end of this period, which may have included prolonged in-hospital stays, multiple surgical and radiologic interventions, frequent visits to health care facilities as outpatients, and an overriding focus on their medical disability, patients are invariably physically deconditioned and emotionally fatigued. The impact on the long-term quality of life, as measured by objective questionnaires, even in those treated, continues to be lower than matched controls, especially if there is a concurrent medical illness. Physical and occupational therapists play a role throughout each patient’s hospitalization, but their efforts become even more important during the healing phase as the focus shifts to reintroducing the patient to normal activities of daily living. Involvement of case management staff early in the patient’s course will identify obstacles to the patient’s successful reintroduction to an active lifestyle, while use of psychiatric consultation-liaison services will identify and address issues of depression and adaptive disorders.

Finally, active involvement by the senior surgeon responsible for the patient’s care to ensure clear communication to the patient and the family during what is invariably a prolonged convalescence and rehabilitation period is essential. Optimally, this physician-patient relationship would have begun early in the patient’s illness and would continue through until complete recovery occurs.
CONCLUSION

Enteric fistulas, occurring spontaneously or in the postsurgical period, represent a significant management challenge. This chapter has focused predominantly on the postsurgical enterocutaneous fistulas, which may result in both morbidity and occasionally mortality for the patient. The care in these patients may be complex and has led to the establishment of specialized intestinal failure units, aimed at optimizing outcome. General principles of care include (1) early recognition and stabilization of patients with fistulas combined with control of sepsis and provision of nutritional support; (2) investigation of the anatomic and etiologic characteristics of each fistula, thus providing information about the likelihood of spontaneous closure or need for operative management; (3) decision making regarding the approach to management that includes the involvement of a multidisciplinary team, which will provide the best possibility of resolution of the fistula; (4) definitive surgical therapy in a controlled setting; and (5) postoperative care including physical rehabilitation and emotional support, which together help patients return to their premorbid condition.

ACKNOWLEDGMENT

We thank Jo Hoeflok, Nurse Practitioner/Enterostomal Therapy Nurse, St. Michael’s Hospital, Toronto, Ontario, Canada, for providing the photographs shown in Figures 16-2 through 16-5.

REFERENCES


OVERVIEW

Acute gastrointestinal (GI) bleeding is a common problem causing significant morbidity and mortality. The source of GI bleeding can be anywhere in the GI tract, from the esophagus to the rectum. GI bleeding is classified into upper or lower bleeding based on the site of bleeding relative to the ligament of Treitz. Upper GI hemorrhage occurs from sites proximal to the ligament of Treitz and accounts for more than 80% of acute bleeding.\(^1\) Lower GI bleeding originates distal to the ligament of Treitz, most commonly from the colon. The small intestine is the site of bleeding in less than 5% of patients.\(^1\) Hemorrhage persisting or recurring after negative endoscopy is termed obscure bleeding. Occasionally patients present with occult bleeding, where there are no signs of overt bleeding but only symptoms of chronic blood loss anemia. In all cases, thorough investigation to localize the source of bleeding allows rapid and often definitive management.
Incidence and Economic Impact of GI Bleeding

Acute GI hemorrhage is one of the most common problems prompting outpatient, emergency room (ER), and inpatient visits. In 2012, nearly 800,000 patients seen in the emergency department (ED) were discharged with a diagnosis of GI hemorrhage, or 254 visits per 100,000 adults. Of those patients, 54.6% were admitted, and over 500,000 patients had GI bleeding as their principal diagnosis for admission in 2012, with an estimated cost of nearly $5 billion US. The incidence of acute upper GI bleeding is estimated at 170 cases per 100,000 adults, and increases with age, affecting 1% of those older than age 85, and is more frequent than lower GI bleeding. There are geographical variations in the GI bleeding incidence, with reported rates varying from 45 per 100,000 in the Netherlands to 172 per 100,000 in Scotland. This difference is likely related to differences in population demographics and prevalence of various etiological factors between the countries.

Morbidity and Mortality

Despite advances in therapy, mortality from GI bleeding remains high. In hospital death from GI bleeding in 2012 occurred in 2.2% of cases, and is particularly high in the elderly. Mortality from GI bleeding occurs frequently on presentation in the ED or early in hospitalization. Evidence suggests that upper GI bleed mortality rates have declined in the last 3 decades, with mortality rates based on the NHDS trending from 4.8% in 1979 to 1989 to 3.1% from 2000 to 2009, primarily due to reductions in early hospital mortality.

INITIAL ASSESSMENT AND RESUSCITATION

A structured approach is recommended in the initial evaluation and management of the patient with acute GI bleeding (Fig. 17-1). Early resuscitation with the aim of restoring hemodynamic stability is the initial priority, followed by a careful history and physical examination to help identify the etiology and source of bleeding. Particular attention should be paid to comorbidities and the drug history as this may further complicate
management. Diagnostic tests are subsequently performed to confirm the site of bleeding, and therapeutic interventions commenced to control active bleeding and prevent future recurrent hemorrhage.


Initial Assessment

Management of resuscitation should follow the principles of A (airway), B (breathing), and C (circulation). Once airway and breathing have been
managed, adequate hemodynamic resuscitation is of the highest priority. In particular, the clinician needs to assess the amount of blood lost and the extent of ongoing bleeding. Initial evaluation should focus on rapid assessment of the magnitude of both the pre-existing deficits and of ongoing hemorrhage. This can be determined by history and examination of the presenting symptoms. In the majority of cases, a wealth of information can be obtained from simple clinical parameters such as consciousness level, blood pressure, and heart rate (Table 17-1), and further facilitated by measurement of urine output as a marker of end-organ perfusion. Not all patients will demonstrate a tachycardic response to bleeding, particularly in the elderly or those on β-blockers. Occasionally severe blood loss may cause vagal-mediated bradycardia. Depending on the hemodynamic status of the patient and existing comorbidities, more invasive forms of monitoring such as central venous monitoring may be required.

<table>
<thead>
<tr>
<th>Class</th>
<th>Blood Loss (mL)</th>
<th>Blood Loss (%)</th>
<th>Heart Rate (bpm)</th>
<th>Blood Pressure</th>
<th>CNS Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;750</td>
<td>&lt;15</td>
<td>&lt;100</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>750–1500</td>
<td>15–30</td>
<td>&gt;100</td>
<td>Orthostatic</td>
<td>Anxious</td>
</tr>
<tr>
<td>III</td>
<td>1500–2000</td>
<td>30–40</td>
<td>&gt;120</td>
<td>Hypotension</td>
<td>Confused</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;2000</td>
<td>&gt;40</td>
<td>&gt;140</td>
<td>Severe hypotension</td>
<td>Obrained</td>
</tr>
</tbody>
</table>

While initial blood tests including a complete blood count and a type and cross are important, a normal hematocrit in the early stages of bleeding may be falsely reassuring, as the hematocrit will only decrease following dilution of the blood volume with resuscitation.

**Resuscitation**

The importance of adequate resuscitation cannot be overemphasized. The most important contributor to morbidity and mortality in acute GI bleeding is fulminant multiorgan failure from inadequate resuscitation. The critical care team should be involved early in the resuscitation process, as early intubation and ventilation will reduce the complications of any respiratory compromise. Large-bore venous access is crucial, particularly in the hemodynamically unstable. Fluid resuscitation should be commenced with an isotonic
crystalloid solution such as lactated Ringer’s. Adequacy of resuscitation should be continuously assessed using clinical parameters such as heart rate, blood pressure, and urine output. A central venous catheter will facilitate assessment of preload in those with cardiac, pulmonary, or renal comorbidities and thereby facilitate more sensitive assessment of fluid balance. Basic laboratory tests including a complete blood count, basic metabolic panel, liver function test, coagulation profile, and type and cross should be obtained.

**Transfusion**

Several factors need to be considered when deciding whether a blood transfusion is required. Of these, the most important are the presence and extent of ongoing bleeding and the response of the patient to fluid resuscitation. Other factors include the age of the patient and the presence of cardiopulmonary comorbidities that might compromise tissue perfusion. The suspected likelihood of rebleeding should also be taken into account; for instance, a transfusion is more likely to be required for esophageal varices, which have a high propensity for profuse rebleeding.

Packed red cells are the usual form of transfusion but are defective in clotting factors, calcium, and platelets. In patients with significant bleeding requiring massive transfusion (more than six units of blood), supplementation of red blood cell (RBC) transfusion with fresh frozen plasma, platelets, and calcium is important. In the trauma literature, use of a 1:1:1 ratio of RBC, plasma, and platelets to approximate whole blood in cases of massive blood loss has been associated with improved outcomes and may be applicable to similar situations due to massive GI hemorrhage.\(^\text{14}\)

In cases of slower bleeding in the hemodynamically stable patient, hematocrit transfusion triggers have changed over time. There is literature from cardiac surgery and orthopedic surgery patients to suggest that a restrictive transfusion strategy may be linked to improved outcomes, primarily due to decreased infectious complications. A hematocrit less than 21 in the young and healthy patient is a threshold where transfusion should be considered, but in older patients with cardiac morbidity, transfusion is recommended at higher values. However, the decision to transfuse should ultimately be guided by the individual patient, taking into account factors such as the degree of ongoing bleeding, potential for recurrent bleeding, and
assessment of tissue perfusion.

**Risk Stratification**

The development of risk stratification scores has facilitated prediction of mortality, risk of rebleeding, and triage for admission and timing of investigations. These scores help differentiate patients stable for outpatient investigation and those requiring admission and urgent endoscopy. The BLEED study identified ongoing bleeding, low blood pressure (systolic blood pressure less than 100 mm Hg), elevated prothrombin time (greater than 1.2 times control), erratic mental status, and unstable comorbid disease as risk factors for significantly higher rates of surgery, increased recurrent bleeding, and higher mortality. Other studies have identified hepatic cirrhosis, high Acute Physiologic and Chronic Health Evaluation II (APACHE II) scores, active GI bleeding, hypotension, and end-organ dysfunction as independent predictors for the above outcomes. These studies highlight the importance of comorbidities in determining the outcome of GI bleeding. For example, one study found a mortality rate of nearly 30% in patients with significant renal disease and 65% in patients with acute renal failure.

**HISTORY AND EXAMINATION**

A thorough history and examination can assist in diagnosing the cause of bleeding and identify comorbidities likely to influence outcome.

**Important Characteristics of GI Bleeding**

Time of onset, volume, and frequency of bleeding are key aspects of the history in determining amount of blood loss. The character of bleeding is extremely important. Hematemesis is defined as the vomiting of blood, and usually represents upper GI bleeding (rarely bleeding from the nasopharynx or oropharynx). Hematemesis may be bright red when fresh, but older blood will resemble coffee grounds. Melena is defined as the passage of offensive, black, tarry stool, again usually due to upper GI bleeding. The appearance of the stool is a result of gastric acid degradation (which converts hemoglobin to
hematin), as well as the effects of intestinal enzymes and bacteria. Rarely, in cases of slow intestinal transit, blood loss from distal small bowel or the right colon may also present as melena. A guaiac test will allow differentiation of the tarry black stool of melena from the dark green stool of patients on iron supplementation (melena will test positive). Bright red blood per rectum is called hematochezia—this may represent blood on the tissue paper, blood around the stool, or blood mixed in with the stool—all important features to elicit on history-taking. Hematochezia usually results from bleeding from the distal colon, usually sigmoid colon or rectum, but may also occur from massive upper GI bleeds with rapid intestinal transit.

**Other Essential Features in the History**

Other useful features to elicit in the history include antecedent vomiting (suggesting a Mallory–Weiss tear), recent weight loss or loss of appetite (suggesting malignancy), recent epigastric pain (possibility of peptic ulceration), and alcohol intake or liver disease (likelihood of variceal bleeding). Demographic data will assist in narrowing down the cause of bleeding—diverticulitis, angiodyplasias, malignancy, and ischemic colitis are likely culprits in the elderly. Younger patients are more likely to bleed from peptic ulceration, Meckel diverticula, hemorrhoids, or esophageal varices. In patients presenting with occult bleeding, the history may reveal syncope, angina, or myocardial infarction related to anemia. Previous abdominal surgery is relevant—previous aortic surgery in particular should raise suspicion of aorto-enteric fistula, and patients with gastrojejunual anastomosis, such as after gastric bypass, are susceptible to marginal ulceration. Drug history is particularly relevant in upper GI bleeding. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common cause of peptic ulceration, and similarly, salicylates and selective serotonin-reuptake inhibitors (SSRIs) are associated with upper GI bleeding. Use of anticoagulants may require reversal with blood products.

**PHYSICAL EXAMINATION**

Bleeding from the nasopharynx and oropharynx may occasionally present as GI bleeding, so these sites should be routinely examined. Pigmented lesions
in the oral mucosa suggest Peutz–Jegher disease—a rare cause of GI bleeding. The abdomen should be examined to identify any masses or hepatosplenomegaly. A tender epigastrium may suggest peptic ulcer disease. The neck and groins should be examined for lymphadenopathy suggestive of malignancy. The examination should include inspection for stigmata of liver disease. The jaundiced patient with ascites, caput medusae, and palmar erythema presenting with GI bleeding should raise suspicion for variceal hemorrhage. Rectal examination and anoscopy are other essential aspects of the examination to exclude rectal cancer or, more commonly, hemorrhoids.

IDENTIFYING THE SOURCE OF BLEEDING

Performing a nasogastric (NG) tube lavage is an important diagnostic maneuver to help localize GI bleeding. An NG aspirate positive for fresh or old blood (either fresh blood or coffee grounds) confirms upper GI bleeding, aids in assessing the rate of bleeding, and allows removal of blood to facilitate endoscopic evaluation of the gastric mucosa during esophagogastroduodenoscopy (EGD).

A nonbilious, non-bloody aspiration of the stomach does not rule out bleeding from the duodenum, as a competent pylorus will prevent reflux of bile or blood into the stomach. A bilious aspirate without blood does suggest a lower GI source for the bleeding. However, a recent study showed that 20% of patients had a blood-free aspirate from the duodenum despite a diagnosis of upper GI bleeding.20

Endoscopy in Upper GI Bleeding

EGD remains the gold standard investigation for the diagnosis and management of upper GI bleeding. EGD facilitates identification of the source of bleeding, determining the underlying etiology, achieving hemostasis, and providing prognostic information for risk stratification.21 The timing of endoscopic assessment in patients with GI bleeding remains controversial. Although there is little doubt that early endoscopy in hemodynamically unstable patients is necessary, the ideal timing for endoscopic intervention in stable patients remains less clear. A review of studies examining the utility of early endoscopic intervention in upper GI
bleeding concluded that while endoscopy within 24 hours of presentation was of benefit in terms of aiding risk assessment and reduced length of hospital stay, earlier endoscopies (within 12 hours) offered no additional benefit. Indeed, endoscopy within 12 hours of presentation was associated with unnecessarily increased use of therapeutic endoscopy without any benefit in terms of rate of rebleeding or survival. Overall, these studies suggested that endoscopy should be performed within 24 hours of presentation, and in hospitals without a 24-hour endoscopy service, this should be offered to patients the following day.\textsuperscript{22}

Other issues should be considered regarding the use of EGD in acute GI bleeding. First, the sensitivity of EGD may be reduced in the presence of active bleeding, as mucosal visibility is impaired. Also, endoscopic complications such as perforation and aspiration increase in the emergency setting. Similarly, sedative medications administered during endoscopy can exacerbate hypotension and hypoxemia. Resuscitative measures should not be delayed or paused for the endoscopic procedure. All patients undergoing urgent endoscopy should be continuously monitored, and consideration given to early anesthesia consultation.

**Endoscopy in Lower GI Bleeding**

**FLEXIBLE SIGMOIDOSCOPY AND COLONOSCOPY**

Colonoscopy is recommended over flexible sigmoidoscopy in lower GI bleeding with few exceptions. Colonoscopy has been deemed the most appropriate investigation in patients over 50 years of age with hematochezia or iron deficiency anemia. In younger patients, colonoscopy can be omitted if a convincing benign source of bleeding has been demonstrated on flexible sigmoidoscopy but should be pursued in cases of repeated bleeding.\textsuperscript{23}

Colonoscopy has a diagnostic yield of 89\% to 97\% in the setting of acute GI bleeding.\textsuperscript{24,25} Bowel preparation using polyethylene glycol with a prokinetic such as metoclopramide has been recommended to improve endoscopic visualization and thus diagnostic yield.\textsuperscript{23,26} This step may have to be omitted in patients with severe ongoing GI bleeding, where there is insufficient time for a formal bowel preparation routine.
Capsule Endoscopy and Deep Enteroscopy

Endoscopic access to the small bowel is difficult, secondary to the length of the small bowel, intraperitoneal location, and contractility. Capsule endoscopy has emerged as a suitable option for small bowel imaging, and is now the third diagnostic test in patients with obscure bleeding following EGD and colonoscopy. Capsules are swallowed that contain a camera that visualizes mucosal surface as it travels the intestine, and wirelessly transmits images for later review. A device is available for patients with dysphagia, dysmotility disorders, and children to deliver the capsule directly to the duodenum. Capsule endoscopy has better yield than push enteroscopy or small bowel series, and an equivalent yield to intraoperative enteroscopy without the morbidity and mortality of the operative procedure. Capsule endoscopy is unsuitable for imaging of the proximal duodenum due to poor visualization of the periampullary region, and should not be performed in those with bowel obstruction or strictures. Yield of capsule endoscopy is dependent on the experience of the reader.

Techniques have been developed to allow endoscopy of the small bowel, including single balloon, double balloon, and spiral enteroscopy. The first two techniques use balloons to grip the intestinal wall and facilitate advancement of the endoscope through the intestine. Spiral enteroscopy uses a special overtube with helices at the distal end to pleat the small bowel onto the overtube, again allowing advancement of the endoscope through the intestine. The advantage of deep, or “push,” enteroscopy is the ability to perform biopsies, treat bleeding, and perform other therapeutic maneuvers. The most significant disadvantage of deep enteroscopy over capsule endoscopy is the risk of perforation (0.3% to 3.4%), particularly in patients with inflammatory bowel disease, malignancy, and bowel anastomosis.

Angiography

Visceral angiography is a relatively insensitive investigation, able to detect bleeding only at a rate of 0.5 to 1 mL/min. Although the specificity approaches 100%, the sensitivity varies from 47% with acute lower GI bleeding to 30% with recurrent bleeding. Angiography has a role in patients with massive lower GI bleeding precluding endoscopic visualization or in
patients with negative endoscopies. Like endoscopy, angiography offers the advantage of potential simultaneous therapeutic intervention.

**Red Cell Labeling (Nuclear Scintigraphy)**

Red cell labeling has been found to play a limited role in the diagnosis of GI bleeding and may be useful after other methods have failed. While sensitive (this method can detect GI bleeding at a rate of 0.1 mL/min), the site of bleeding is localized to an area of the abdomen rather than a portion of the GI tract. Intestinal motility can shift intraluminal blood away from the site of bleeding, resulting in incorrect localization. Specificity is improved when scans are positive within 2 hours after injection of labeled erythrocytes, as less transit through the bowel will have occurred, with accurate localization in 95% to 100% of cases. Correct localization falls to 57% to 67% when scans are positive more than 2 hours after injection.\textsuperscript{40} Red cell scans are therefore more often used to identify a potential role for subsequent angiography. In patients with negative red cell scans or scans positive only after 2 hours, angiography is unlikely to be positive.

**CT Angiography**

CT angiography (CTA) is a promising new technique that offers advantages compared to tagged RBC scanning. With the dissemination of high-resolution CT scanners, a CTA is available widely and at all times of the day and night. While nuclear RBC scanning takes hours to perform, a CTA can be obtained in minutes. A recent non-randomized retrospective study of patients who received either a tagged RBC scan or a CTA prior to visceral angiography showed that CTA was better at localizing the site of GI bleeding.\textsuperscript{41} Despite increased use of IV contrast in CTA patients, no adverse impact on renal function was demonstrated. CTA has been reported to detect blood loss as low as 0.4 mL/min, which would make it less sensitive than nuclear RBC scanning. Further studies are still required to determine the role of CTA in assessing GI bleeding.

**THERAPEUTIC OPTIONS**
Pharmacologic Management

Pharmacologic management is unlikely to halt active bleeding but is aimed at preventing recurrent bleeding. Proton pump inhibitors, but not H2 blockers, have been shown to reduce recurrent bleeding from gastric ulcers, as clot formation is stabilized in the absence of gastric acid. Octreotide is useful in variceal bleeding and may have an adjunctive role in other upper GI bleeds (see variceal bleeding below). Triple therapy treatment for *Helicobacter pylori* can prevent recurrent ulcers and bleeds.

Endoscopic Treatment

Endoscopy remains the mainstay of investigation and therapy for most causes of upper and lower GI bleeding. Techniques used for control of hemorrhage include thermal coagulation, injection therapy, and mechanical devices such as metallic clips and band ligation. Thermal coagulation probes include bipolar, monopolar, and heat probes, with an overall perforation rate of up to 2.5%, particularly frequent in the thin-walled right colon. Argon plasma coagulation is a means of non-contact coagulation with an almost nonexistent risk of perforation in the colon. Laser-mediated coagulation (such as with the Nd:YAG laser) uses high-energy laser light to vaporize the tissue, producing deeper penetration than argon plasma coagulation but with a higher perforation rate.

Injection of a 1:10,000 dilution of epinephrine is an effective and inexpensive method of endoscopic treatment, causing vasoconstriction and physical compression of the vessel. Metallic clips, in both reusable and disposable forms, are used to control hemorrhage endoscopically. Rubber band ligation is frequently employed in lower GI bleeding due to hemorrhoids or rectal varices.

Interventional Angiography

While initial attempts of embolization led to high rates of bowel infarction due to the use of large-bore catheters for cannulation, current approaches with microcatheters have produced success rates of 70% to 90% without significant complications, and recurrent hemorrhage rates of only 15%.
Embolization materials include microcoils, gelfoam, and polyvinyl alcohol particles. Selective angiographic embolization has been shown to arrest life-threatening bleeding from gastroduodenal ulcers, with a low rate of early rebleeding and no late rebleeding, obviating the need for emergency surgery in high-operative-risk patients.\textsuperscript{45}

Early bleeding recurrence is associated with coagulation disorders, longer time to angiography, higher preprocedural blood transfusion volume, two or more comorbidities, and the use of coils as the only embolic agent.\textsuperscript{46} Embolization has been shown to have 85% success rate in patients with diverticular lower GI bleeding, with higher efficacy in the left compared to right colon. Angiography is less efficacious in non-diverticular lower GI bleeding (e.g., arteriovenous dysplastic lesions) with a greater than 40% rate of rebleeding.\textsuperscript{47}

Angiography may also be coupled with selective infusion of a vasoconstrictor such as vasopressin, or the longer-acting analogue terlipressin. However, this strategy is associated with a 50% rate of rebleeding after cessation of the infusion.\textsuperscript{48} The side effects of vasopressin and terlipressin, including abdominal pain and cardiac complications, have meant that this technique is now only rarely used.

**Surgery**

Surgery is usually reserved for therapy when less invasive therapeutic modalities have failed and bleeding has been clearly localized. Surgery does remain the treatment of choice in patients with malignant or benign tumors, and may also be used as a last resort in patients with recurrent bleeding without a defined bleeding point or in fulminant hemorrhage. Further discussion of surgical options is detailed in relevant sections below.

**UPPER GI HEMORRHAGE**

**Causes of Upper GI Hemorrhage**

Causes of upper GI hemorrhage can be divided into variceal and non-variceal bleeding, which accounts for 80% to 90% of acute upper GI bleeding (Table
Even in patients with portal hypertension, non-variceal bleeding is still more common. However, due to its morbidity and mortality, if suspected, variceal bleeding should be excluded first.

**TABLE 17-2: CAUSES OF UPPER GI BLEEDING**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-variceal upper GI bleeding</strong> (80%)</td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>40%</td>
</tr>
<tr>
<td>Mallory–Weiss tears</td>
<td>15–20%</td>
</tr>
<tr>
<td>Gastritis/Duodenitis</td>
<td>10–15%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>5–10%</td>
</tr>
<tr>
<td>Dieulafoy lesions</td>
<td>1.5%</td>
</tr>
<tr>
<td>GAVE</td>
<td>4%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2%</td>
</tr>
<tr>
<td>Others:</td>
<td></td>
</tr>
<tr>
<td>Aorto-enteric fistula</td>
<td></td>
</tr>
<tr>
<td>Hemobilia</td>
<td></td>
</tr>
<tr>
<td>Hemosuccus pancreaticus</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic bleeding</td>
<td></td>
</tr>
<tr>
<td><strong>Portal hypertensive upper GI bleeding</strong> (20%)</td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal varices</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Gastric varices</td>
<td>Rare</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**NON-VARICEAL BLEEDING**

**Peptic Ulcer Disease and Bleeding.** Gastroduodenal peptic ulceration accounts for 40% of all non-variceal upper GI bleeding.\(^{20}\) The introduction of *H pylori* eradication therapy and proton pump inhibitors has reduced the incidence of peptic ulcer disease (PUD), leading to reduced rates of operation and mortality from PUD. However, the overall incidence of peptic ulcer bleeding remains high, with significant associated mortality and cost.\(^{49,50}\)

A large proportion of PUD bleeding is linked to use of aspirin and
NSAIDs, and the majority of cases occur in the elderly (68% of patients are over 60 years of age and 27% over 80 years of age). Ten percent to 15% of ulcers will bleed at some point during the course of the disease. Patients with bleeding ulcers commonly present with hematemesis and/or melena. History, examination, and investigations should proceed as outlined earlier (Fig. 17-2). Duodenal ulcers are more common, but gastric ulcers usually bleed more profusely. Ulcers involving an artery such as branches of the gastroduodenal or left gastric arteries can bleed significantly.

**FIGURE 17-2** An algorithm for the management of peptic ulcer bleeding.

Several risk stratification scores have been developed to assist in identification of patients who require close monitoring and are at risk of rebleeding. The two most commonly used tools are the Rockall score and the Blatchford score (Table 17-3). The Rockall score utilizes clinical as well as endoscopic findings to risk-stratify patients. The score ranges from 0 to 11, with a higher score indicating a greater risk of rebleeding or death. The
Blatchford score incorporates clinical and laboratory values to produce a maximum score of 23, with higher scores again associated with a greater likelihood of rebleeding or death.\textsuperscript{53}

**TABLE 17-3: COMPARISON OF THE BLATCHFORD AND ROCKALL SCORES**

<table>
<thead>
<tr>
<th>Criteria of the Blatchford Score</th>
<th>Criteria of the Rockall Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>Age</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>Shock</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Coexisting illness</td>
</tr>
<tr>
<td>Pulse</td>
<td>Endoscopic diagnosis</td>
</tr>
<tr>
<td>Melena</td>
<td>Endoscopic stigmata of recent</td>
</tr>
<tr>
<td>Syncope</td>
<td>hemorrhage</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
</tr>
</tbody>
</table>

The endoscopic appearance of a bleeding ulcer alone can also be used to stratify the risk of rebleeding using the Forrest criteria\textsuperscript{54} (Table 17-4). High-grade lesions are those which are actively spurting or oozing blood, or have a non-bleeding visible vessel or adherent clot.

**TABLE 17-4: FORREST CLASSIFICATION FOR ENDOSCOPIC FINDINGS AND RISK OF REBLEEDING IN PU DISEASE**
**Medical Management**

**STOP ANY CAUSES; EG, DRUGS.** All ulcerogenic medication such as salicylates, NSAIDs, and SSRIs should be stopped and non-ulcerogenic alternatives prescribed. COX-2 inhibitors which initially showed promise as a gastroprotective alternative to NSAIDs have recently been shown to demonstrate cardiotoxicity without significant benefit on gastric mucosal protection and are therefore infrequently used.\(^5^5\)

**ERADICATION OF *Heliocobacter pylori* AND LONG-TERM ACID SUPPRESSION.** The association of bleeding with *H pylori* infection is not as strong as the association reported for perforated ulcers, with *H pylori* infection reported in only 60% to 70% of bleeding ulcers. However, recent data show that treating patients positive for *H pylori* with eradication therapy reduces the risk of rebleeding and obviates the need for long-term acid suppression, hence eradication with triple therapy is recommended in all bleeders infected with *H pylori*.\(^5^6\)

Gastric acid has been shown to impair clot formation, promote platelet disaggregation, and increase fibrinolysis. In keeping with this, proton pump inhibitors have been shown to significantly reduce the risk of ulcer rebleeding, the need for urgent surgery and, in patients with high-risk stigmata who have undergone endoscopic therapy, mortality.\(^5^7,5^8\)
Endoscopic Management. Patients with high-risk stigmata on endoscopy (active bleeding or non-bleeding visible vessel) require hemostatic intervention, such as injection or thermal or mechanical therapy, such as clips (Fig. 17-3). Addition of any one of these to adrenaline injection further reduces rebleeding rates, the need for surgery, and mortality.\textsuperscript{59–61}

FIGURE 17-3 Metallic clips to arrest bleeding from a duodenal ulcer. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)

Several factors are predictors of failure of endoscopic therapy for peptic ulcer bleeding, including previous ulcer bleeding, shock on presentation, active bleeding during endoscopy, ulcers >2 cm in diameter, a large underlying bleeding vessel ≥2 mm in diameter, and ulcers on the lesser curve of the stomach or the posterior or superior duodenal bulb.\textsuperscript{62} Recent studies suggest that second-look endoscopy (within 24 hours of the initial endoscopic therapy) provided only a small reduction in the rate of rebleeding, is not cost-effective in the presence of acid-suppressing medication, and is overall not recommended.\textsuperscript{21,63,64} Repeat endoscopy should only be considered in cases of recurrent hemorrhage or unsuccessful first treatment.
**Surgical Management.** Meta-analysis and surgical registry data show the rate of surgical intervention for bleeding peptic ulcers has decreased with time. An improved understanding of peptic ulcer disease as well as the development of newer pharmacologic and endoscopic treatments has meant that surgery is now employed not as first-line or curative treatment but instead only when other modalities have failed.

There are no consensus guidelines on the appropriate indications for surgery. In general, persistent blood loss with failure of endoscopic therapy and a blood transfusion requirement in excess of six units is often considered an indication for surgical intervention (Table 17-5). Similarly, hypovolemic shock associated with recurrent hemorrhage or slow continuous blood loss requiring ongoing transfusion are also considered indications. Shock on admission, an elderly patient, severe comorbidity, a rare blood type, refusal of transfusion, and bleeding chronic gastric ulcer with a suspicion of malignancy are considered relative indications for surgery.

**TABLE 17-5: POSSIBLE INDICATIONS FOR SURGICAL INTERVENTION FOR PU BLEEDING**

<table>
<thead>
<tr>
<th>Absolute indications</th>
<th>Persistent blood loss refractory to endoscopic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock with recurrent hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Slow blood loss requiring more than 3 units blood transfusion per day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative indications</th>
<th>Shock on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transfusion in excess of 6 units</td>
</tr>
<tr>
<td></td>
<td>Elderly patient</td>
</tr>
<tr>
<td></td>
<td>Severe comorbidity</td>
</tr>
<tr>
<td></td>
<td>Rare blood type/ refusal of transfusion</td>
</tr>
<tr>
<td></td>
<td>Suspicion of malignancy in a gastric ulcer</td>
</tr>
</tbody>
</table>

In stable patients with evidence of rebleeding, a second attempt at
endoscopic hemostasis is often as effective as surgery with fewer complications, and is the recommended management.\textsuperscript{65} The aim of surgery in both gastric and duodenal ulcers is to arrest hemorrhage and perform an acid-reducing procedure if deemed necessary.

**Operative Procedure for Duodenal Ulcers.** A longitudinal duodenotomy or duodenopyloromyotomy provides good exposure of bleeding sites in the duodenal bulb, the most common location of duodenal ulcers. Direct pressure provides temporary arrest of the bleeding, and should be followed by suture ligation of the bleeding vessel. Four-quadrant suture ligation will achieve hemostasis in anterior ulcers. Posterior ulcers, particularly if involving the pancreaticoduodenal or gastroduodenal artery, will require suture ligation of the artery both proximal and distal to the ulcer for adequate control of hemorrhage, as well as placement of a U-stitch underneath the ulcer to control the pancreatic branches (Fig. 17-4).
FIGURE 17-4  Suture control of bleeding duodenal ulcers. A longitudinal pyloric incision is made and figure-of-eight sutures are placed at the cephalad and caudal aspects of the ulcer to occlude the gastroduodenal artery.

The use of an acid-reducing procedure in duodenal ulcers remains a topic of debate, as theoretically arrest of hemorrhage and *H pylori* eradication is likely to be sufficient management. There is no good data on which to base recommendations, and currently the decision is left to the surgeon’s
judgment, taking into account both individual patient factors and the surgeon’s experience with these operations. Surgical options for acid reduction in bleeding duodenal ulcer management include pyloroplasty with truncal vagotomy, parietal cell vagotomy, or antrectomy with truncal vagotomy. Truncal vagotomy with pyloroplasty is most frequently employed, as it is facilitated by the duodenotomy already made to control hemorrhage. Experience with parietal cell vagotomy is limited in the current era. Antrectomy with truncal vagotomy may be considered in the stable patient with refractory PUD but is a more complex procedure with increased morbidity and mortality. Ulcer surgery is covered in greater detail in Chapter 35, Stomach and Duodenum: Operative Procedures.

Operative Procedure for Gastric Ulcers. Unlike the duodenal ulcer, gastrotomy with oversewing of bleeding is not adequate surgical treatment due to a high risk of rebleeding and underlying malignancy in gastric ulcers. A distal gastrectomy for ulcers of the antrum and distal stomach is the surgical treatment of choice. Resection of the ulcer alone is associated with a 20% rebleeding rate, but can be considered in combination with an acid-reducing procedure (eg, vagotomy and pyloroplasty) in patients who cannot tolerate a formal gastrectomy. Management of bleeding ulcers at the cardioesophageal junction and the proximal stomach is challenging. Formal resection with a proximal or near-total gastrectomy carries high morbidity and mortality in patients acutely bleeding. In these cases, less aggressive operations, such as distal gastrectomy with resection of a tongue of proximal stomach to excise the ulcer, wedge resection of the ulcer, or simple oversewing with a vagotomy and pyloroplasty, can be considered.

Mallory–Weiss Tears. Mallory–Weiss tears are lacerations of the esophagus or stomach caused by severe vomiting. With vomiting, the diaphragm moves abruptly upward, intra-abdominal pressure increases, and the gastric cardia is forced into the thorax through the diaphragmatic hiatus. Hiatus hernias coexist in more than 75% of patients with Mallory–Weiss tears, and the amount of herniated stomach determines the point of maximal dilatation (law of Laplace) and therefore the position of the tear. Large hiatus hernias are associated with more distal tears, while in patients with small or absent hiatus hernias, tears occur at or below the gastroesophageal junction. The majority of tears are situated within 2 cm of the gastroesophageal
junction on the lesser curvature.

The highest incidence of Mallory–Weiss tears occurs in patients between 30 and 50 years of age, and in males more than females. Forty percent to 75% of patients have a history of alcohol use and 30% have a history of aspirin use. Patients typically present with a history of several episodes of vomiting or retching followed by hematemesis with fresh red blood. Ten percent of patients may present with only melena.

EGD usually identifies a single tear on the lesser curve of the cardia, or occasionally on the greater curvature of the cardia. Retroflexion during the endoscopic examination is an important maneuver in these patients to ensure the distal gastroesophageal junction and cardia are visualized. The majority of lesions heal spontaneously, hence management is largely supportive, with emphasis on antiemetic and acid suppression. Patients with persistent bleeding may require endoscopic or angiographic intervention. Surgery may be required should these options prove unsuccessful, and hemorrhage can be arrested operatively by a high gastrotomy and suture of the mucosal laceration.

**Cameron Lesions.** A rare cause of upper GI bleeding is an erosion or ulcer of the stomach that occurs within a hiatal hernia. These have been reported to occur in up to 5% of patients with hiatal hernias, although they are overall an uncommon source of GI bleeding. Accurate diagnosis of a Cameron lesion requires an experienced endoscopist. The etiology of the ulcer is thought to be related to a combination of mechanical trauma of the gastric wall moving through the hiatus, exacerbated by reflux esophagitis. Treatment involves repair of the paraesophageal or hiatal hernia.

**Stress-Related Mucosal Bleeding.** Critically ill patients are at risk for the development of diffuse mucosal injury of the stomach, resulting in upper GI bleeding with significant morbidity and mortality. This phenomenon, termed “stress-related mucosal bleeding” or “stress gastritis” is a result of a combination of mucosal ischemia and reperfusion injury and impairment of host cytoprotective defenses. The most important risk factors for stress-related mucosal bleeding are prolonged mechanical ventilation (>48 hours) and coagulopathy. Other risk factors include shock, severe sepsis, neurological injury/neurosurgery, >30% burns, and multiorgan failure. Patients with these factors should receive prophylaxis with antacids, H2-
receptor blockers, proton pump inhibitors, or carafate.

The incidence of clinically significant stress gastritis, a previously common problem, has been reduced with introduction of proton pump inhibitor prophylaxis. Acid suppression is often sufficient to control hemorrhage in stress-related mucosal bleeding. For persistent bleeding, options include selective infusion of octreotide or vasopressin via the left gastric artery, endoscopic measures, or angiographic embolization. Surgery is now rarely required, but if necessary, involves vagotomy and pyloroplasty with oversewing of discrete regions of hemorrhage or subtotal gastrectomy.

**Esophagitis.** Esophageal bleeding is rare and most commonly occurs due to esophagitis. Gastroesophageal reflux disease (GERD) is the most common cause, with acid damage to the esophageal mucosa resulting chronic inflammation and bleeding (Fig. 17-5). Other causes of esophagitis include Crohn’s disease, drugs, radiotherapy, and infectious etiologies in the immunocompromised. Infective esophagitis is uncommon but may lead to torrential hemorrhage. Pathogens include herpes simplex, Candida, cytomegalovirus, HIV, Epstein–Barr virus, and secondary involvement of the esophagus in mycobacterial infection of adjacent lymph nodes.
Management, particularly of GERD-induced esophagitis, hinges on acid-suppressive therapy, occasionally requiring therapeutic endoscopy to arrest the bleeding. For infectious esophagitis, identifying and treating the underlying infectious cause is often successful at stopping bleeding.

**Dieulafoy Lesion.** Dieulafoy lesions are an arterial vascular anomaly featuring abnormally large (“caliber-persistent”) submucosal end arteries, likely congenital in origin, with the potential for massive, potentially life-threatening hemorrhage upon erosion of the overlying mucosa. These lesions are most commonly located in the stomach within 5 to 7 cm of the cardia, but may present in the small bowel and colon. They account for 1.5% of upper GI bleeding and are more common in men.\(^{73}\)

Dieulafoy lesions appear as reddish-brown protrusions on endoscopy with no ulceration. Endoscopic therapy is often successful, with clipping or banding demonstrated to be superior to injections.\(^{74,75}\) Angiographic embolization or surgery may be necessary for endoscopic failures. Prior
endoscopic tattooing facilitates identification of the site of the lesion for resection if surgery is necessary.

**Gastric Antral Vascular Ectasia.** Gastric antral vascular ectasia (GAVE), or “watermelon stomach,” is named for the dilated, tortuous mucosal capillaries and veins in the gastric antrum that converge onto the pylorus and resemble the surface of a watermelon ([Fig. 17-6](#)). This condition is more common in women and usually presents with occult blood loss and iron deficiency anemia. Argon plasma coagulation (APC) is the treatment of choice and may need to be repeated. Proton pump inhibitor cover is recommended for 1 month following treatment.\(^73,76\) Patients refractory to APC should be considered for surgical intervention, usually an antrectomy.

**FIGURE 17-6** Gastric antral vascular ectasia (GAVE) can be seen in the gastric antrum, giving the stomach a watermelon appearance. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)

**Malignancy.** Malignant upper GI lesions rarely present with significant overt hemorrhage, and more commonly present with hemoccult-positive stool or
iron deficiency anemia. Endoscopy occasionally reveals a recurrent bleeding ulcer, a common feature of GI stromal tumors, which characteristically appears as a submucosal tumor with central umbilication and ulceration (discussed further in Chapter 33, Gastrointestinal Stromal Tumors), and on occasion leiomyomas and lymphomas (Fig. 17-7). Surgery is the therapy of choice and may involve either curative resections or in unfit patients, palliative wedge resections.

![A gastrointestinal stromal tumor (GIST) of the stomach on endoscopy. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)](image)

**FIGURE 17-7** A gastrointestinal stromal tumor (GIST) of the stomach on endoscopy. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)

**Aortoenteric Fistula.** Aortoenteric fistula is an important clinical condition that can cause torrential GI hemorrhage. Primary fistulae are rare; fistulation occurs most commonly following a previous abdominal aortic aneurysm (AAA) repair, and is seen in approximately 1% of these cases. The pathophysiology behind this is likely to be infective in origin, leading to the development of a pseudoaneurysm at the proximal suture line with subsequent fistulization into the adjacent duodenum (Fig. 17-8).
FIGURE 17-8 Intraoperative appearance of an aortoenteric fistula. The photograph demonstrates a large hole (black arrow) in the posterior aspect of the 3rd part of the duodenum after it was medialized and peeled off of the graft. The photograph has been taken from left side of the table with the patient in supine position. (Used with permission from Neal Barshes, MD, MPH, Brigham and Women’s Hospital, Boston, MA.)

Early diagnosis of this problem is critical but requires a high index of suspicion in patients presenting with GI bleeding with known aortic aneurysms or a history of aortic aneurysm repair. Often, patients present with smaller, self-limiting episodes of GI hemorrhage (“sentinel bleeds”). Urgent endoscopy at this stage is essential to preempt a subsequent torrential, often fatal bleed, and usually reveals bleeding at the third or fourth part of the duodenum (Fig. 17-9). CT with IV contrast is a useful adjunct in these patients, often demonstrating air within the aortic thrombus or around the graft (particularly in the context of an infected graft), and rarely a pseudoaneurysm or contrast within the duodenal lumen.
Surgical repair involves extra-anatomic bypass grafting and aortic ligation for primary aorto-enteric fistula. For secondary aorto-enteric fistula, surgery involves excision of the graft with extra-anatomic bypass or in situ aortic reconstruction. By necessity, these procedures are often performed in critically ill, septic patients and are hence associated with high morbidity and mortality. Endovascular stenting has been explored as treatment for aorto-enteric fistulas but has been linked to a high incidence of recurrent bleeding and infection, particularly in the presence of preprocedural infection.\textsuperscript{77}

\textbf{Hemobilia.} Hemobilia is a rare cause of GI bleeding. Causes include trauma, hepatic neoplasms, instrumentation of the biliary tree, percutaneous radiofrequency liver ablation, and prior liver transplantation. A high index of suspicion is required in patients with these risk factors, as the classical presentation of hemorrhage, right upper quadrant pain, and jaundice is only seen in a minority of patients. Endoscopy may reveal blood at the ampulla,
but angiography and embolization remains the diagnostic and therapeutic modality of choice.

**Hemosuccus Pancreaticus.** Bleeding from the pancreatic duct (hemosuccus pancreaticus) is another rare cause of upper GI bleeding, caused by fistulation of a pancreatic pseudocyst into the splenic or other peripancreatic artery.\(^7^8\) A presentation of abdominal pain, hematemesis, and melena in patients with a previous history of pancreatitis should raise suspicion of hemosuccus pancreaticus. Angiography is again both diagnostic and therapeutic, although in some cases distal pancreatectomy may be necessary.

**Iatrogenic Bleeding.** Prior endoscopic or surgical procedures are causes of bleeding. Common endoscopic procedures with bleeding complications include percutaneous gastrostomy tube placement, which carries a 3% rate of GI hemorrhage. Endoscopic retrograde cholangiopancreatography with sphincterotomy is associated with a 2% risk of bleeding. In many cases, bleeding can be controlled endoscopically with injection therapy, and surgical intervention is rarely required. Bleeding following upper GI surgery often occurs from suture or staple lines. These can occasionally be treated endoscopically, with care taken to minimize insufflation and torque to avoid disrupting fresh anastomosis.

**VARICEAL BLEEDING AND PORTAL HYPERTENSION**

Portal hypertension is a serious cause of upper GI bleeding, often related to cirrhosis and chronic liver disease. The pathophysiology of portal hypertension is discussed further in Chapter 61. Approximately 50% of patients with cirrhosis will develop gastroesophageal varices as a result of portal hypertension.\(^7^9\) Variceal bleeding occurs in 30% of patients, and is one of the most important complications of hepatic cirrhosis. Variceal bleeding is associated with increased risk of rebleeding, higher transfusion requirements, greater length of stay, and higher morbidity and mortality compared with non-variceal bleeding.\(^8^0\)

Gastroesophageal varices represent a rise as the portal circulation tries to decompress into the systemic circulation. Other sites of portal-systemic collaterals are the stomach, the umbilical region (caput medusae), and the distal rectum. Isolated gastric varices (IGV) can occur in the absence of
esophageal varices and are found along the gastric fundus (IGV1) or the body, antrum, or pylorus (IGV2).\textsuperscript{79} Risk factors for gastric variceal bleeding include variceal size and the presence of a cherry-red spot (localized reddish mucosal area or spots on the mucosal surface of a varix).\textsuperscript{81}

Besides varices, portal hypertension can lead to portal hypertensive gastropathy—the diffuse dilation of the mucosal and submucosal venous plexus of the stomach with overlying gastritis. The stomach develops a snakeskin appearance with cherry-red spots on endoscopy, and rarely may be the site of major hemorrhage (Fig. 17-10).

\textbf{FIGURE 17-10} Endoscopic view of portal hypertensive gastropathy. Note the snakeskin appearance of the stomach and the associated cherry-red spots. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)
Initial management of variceal upper GI bleeding follows the same principles as that of non-variceal upper GI bleeding, with emphasis on urgent resuscitation and therapeutic endoscopy due to the higher morbidity and mortality associated with variceal bleeds (Fig. 17-11). The diagnosis of variceal hemorrhage is based on meeting one of the following criteria: active bleeding from a varix, a “white nipple” overlying a varix, clots overlying a varix, or varices with no other potential source of bleeding.\textsuperscript{82}
FIGURE 17-11 An algorithm for the management of variceal bleeding.

Management

Medical. Somatostatin or analogues such as octreotide should be administered immediately in cases where there is a high index of suspicion for variceal bleeding, and continued for 3 to 5 days after endoscopic confirmation of diagnosis. Current recommendations are that any patients with cirrhosis and GI bleeding should also be given antibiotic prophylaxis against spontaneous bacterial peritonitis with a fluoroquinolone.

Endoscopic. In suspected variceal bleeding, endoscopy should be performed urgently, particularly in unstable patients. Early endoscopy excludes non-variceal causes of bleeding, which occur in 15% of patients with varices. Variceal ligation is the endoscopic treatment of choice, as it has lower rates of complications compared to sclerotherapy, which can cause perforation, mediastinitis, and stricture formation. Variceal ligation involves the placement of rubber bands to completely interrupt blood flow into the varix. The mucosa and submucosa eventually necroses, the rubber rings slough, and granulation tissue and scar replace the varix. Multiple sequential treatments may be required but will ultimately achieve control of variceal bleeding in up to 90% of patients.

Mechanical tamponade devices may be useful in temporarily controlling esophageal variceal bleeding when other methods have failed. The Sengstaken–Blakemore tube consists of an NG tube with gastric and esophageal balloons which are inflated to compress the esophagogastric venous plexus, arresting bleeding but at the risk of ischemic necrosis and perforation. Deflation of the tube leads to recurrent bleeding in 50% of patients; hence, this technique is reserved as a temporizing measure in massive hemorrhage before definitive therapy.

Gastric varices should be managed initially by pharmacotherapy. Endoscopic therapy is less successful with gastric varices due to the diffuse nature of portal hypertensive gastropathy. Patients with refractory bleeding should be referred early for decompressive therapy such as transjugular intrahepatic portosystemic shunt (TIPS) or shunting.

Isolated gastric varices, without associated portal hypertension, can occur in the setting of splenic vein thrombosis, often associated with pancreatitis.
Varices occur in the presence of normal central portal pressures due to left-sided hypertension, rerouted from the spleen to the short gastric vessels. While splenectomy relieves the hypertension, the risk of variceal bleeding in these patients is low and hence surgery is not routinely undertaken.\textsuperscript{86}

**Prevention of Rebleeding.** Prevention of rebleeding is critical in this patient population. Rebleeding occurs in up to 70\% of patients within 2 months in the absence of definitive therapy.\textsuperscript{87} The greatest risk of rebleeding is in the first few days following the initial episode. A combination of nonselective β-blockers with isosorbide mononitrate has been shown to be more effective than β-blockers alone in preventing rebleeding.\textsuperscript{88} The addition of prophylactic endoscopic band ligation to combination pharmacotherapy did not reduce the risk of rebleeding but instead was associated with more adverse events in a recent randomized controlled trial.\textsuperscript{89}

**Radiologic or Surgical Portal Decompression.** In the approximately 10\% of cases of variceal bleeding where endoscopic management fails, urgent decompression of the portal system is the next step. A TIPS procedure creates an artificial anastomosis between the hepatic and portal veins under fluoroscopic guidance with a covered stent, relieving portal pressure by shunting blood away from the hepatic sinusoids.\textsuperscript{90} TIPS is associated with a 30-day mortality of up to 30\% in the emergency setting, usually due to complications of hepatic encephalopathy.\textsuperscript{91} Rebleeding may occur in 20\% of patients and is often due to TIPS occlusion.

Surgery is another therapeutic option for decompression of the portal system. Surgical shunts, such as the selective distal splenorenal shunt (DSRS), have lower rates of rebleeding compared to endoscopic therapy but do not demonstrate any difference in survival.\textsuperscript{92} DSRS patients have an in-hospital mortality of ~5\%, a 5\% to 8\% rate of rebleeding, and a 75\% to 80\% 3-year survival.\textsuperscript{92} A randomized controlled trial comparing TIPS with DSRS in patients who failed medical or endoscopic therapy showed no significant difference in the rate of rebleeding, hepatic encephalopathy, or overall survival. However, TIPS patients required close follow-up with a higher rate of re-intervention. DSRS may be a more suitable option in patients with limited access to health care facilities.\textsuperscript{93} Further details on surgical decompression for portal hypertension are covered in Chapter 61.
LOWER GI HEMORRHAGE

Lower GI bleeding occurs most commonly from the colon but can arise from any site distal to the ligament of Treitz. Difficulty in diagnosis of lower GI bleeding stems from the large surface area of colon and small intestine, intermittent bleeding, occasional lack of visible mucosal lesions, and difficulties in endoscopic visualization from forward movement of blood. The majority of lower GI bleed patients experience self-limiting episodes; only 10% to 20% of patients present with massive unremitting bleeding. Most lower GI bleeding originates from the colon due to common entities such as diverticular disease and neoplasia (Table 17-6). Early identification of the cause of bleeding is essential for appropriate management, in particular for cases of malignancy.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic bleeding (95%)</td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>30–40%</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>40%</td>
</tr>
<tr>
<td>Ischemia</td>
<td>6–18%</td>
</tr>
<tr>
<td>Anorectal disease</td>
<td>6–16%</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>3–11%</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>3–29%</td>
</tr>
<tr>
<td>Polyps</td>
<td>5–13%</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2–4%</td>
</tr>
<tr>
<td>Radiation proctitis</td>
<td>1–9%</td>
</tr>
<tr>
<td>Other</td>
<td>6–23%</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Small intestinal bleeding (5%)

<table>
<thead>
<tr>
<th>Causes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiodysplasias</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td></td>
</tr>
<tr>
<td>Meckel diverticulum</td>
<td></td>
</tr>
<tr>
<td>Erosions/ulcers</td>
<td></td>
</tr>
<tr>
<td>Crohn's disease</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
</tr>
</tbody>
</table>
Management of Lower GI Bleeding

Lower GI bleeding is often less severe than upper GI bleeding; however, the same principles for initial evaluation and resuscitation should be followed (Fig. 17-12). Accurate identification of the source of bleeding can be difficult in patients with lower GI bleeding—more than one source for bleeding is found in 40% of patients, and in up to 25% of patients no source is identified. A management algorithm is outlined in Fig. 17-13. Hemodynamically stable patients with hematochezia should first undergo colonoscopy to identify a bleeding source. If a bleeding site is identified, endoscopic therapy should be attempted to control the bleeding. If no bleeding site is identified, an EGD should be performed followed by capsule or deep enteroscopy if this is unrevealing. Hemodynamically unstable patients should undergo EGD initially, as severe upper GI bleeding may present as hematochezia.

FIGURE 17-12 An algorithm for the management of lower gastrointestinal bleeding. (Reproduced with permission from Townsend CM, Beauchamp RD, Evers BM, et al:
Patients with bleeding refractory to endoscopic management or those with significant hemodynamic instability may require urgent operative intervention. In these patients, an exploratory laparotomy is performed with attempts made to determine the location of blood within the GI tract. The GI tract should be thoroughly examined for masses and diverticular disease, such as a Meckel diverticulum. On-table enteroscopy and lavage may allow localization of the bleeding source for segmental resection but is best attempted in stable patients who can tolerate the additional procedure length. A segmental bowel resection is appropriate in localized bleeding, and in relatively fit patients this may be combined with a primary anastomosis. In unfit patients with hemodynamic instability, an ostomy with or without a mucous fistula is a more appropriate option. Segmental colectomies should not be performed as “blind” procedures without localization of the bleeding.
source, as these have been associated with high rates of mortality and rebleeding (up to 50% and 75%, respectively). A better alternative in patients without localization of the bleeding source is a “blind” subtotal colectomy, with either an end ileostomy or a primary ileorectal anastomosis, which carries a <10% mortality rate and <10% rebleeding rate.

Causes of Lower GI Hemorrhage

DIVERTICULAR DISEASE

Diverticular disease is a common, often asymptomatic, disease of Western countries. The incidence increases with age; up to 60% of patients over 80 years of age have diverticulae. In Western countries, 95% of diverticulae are in the sigmoid and left colon; however, in Asian countries, 70% of cases are in the right colon. Colonic diverticulae are pulsion-type pseudodiverticulae—outpouchings of the mucosa and submucosa through the muscular layer of the bowel at the sites of penetration of the vasa recta. Only 4% to 17% of patients with diverticular disease develop symptoms of bleeding. However, due to its prevalence, diverticular disease accounts for 30% to 40% of lower GI bleeding. Eighty percent of diverticular bleeds stop spontaneously, but a small minority will require intervention. Ten percent of patients will rebleed within a year and 50% within 10 years.

Colonoscopy remains the most useful diagnostic and therapeutic investigation for diverticular bleeding (Fig. 17-13). When colonoscopy fails, angiographic embolization can be successful in 85% of diverticular bleed patients. Surgery is indicated for refractory bleeding, and colonic resection may be considered as a management option in patients with multiple episodes of self-limiting bleeding.

Angiodysplasia. Angiodysplastic lesions in the intestine are degenerative vascular lesions that develop as a result of progressive dilation of submucosal vessels. Bleeding from these lesions can account for up to 40% of lower GI bleeds. Angiodysplastic lesions are frequently found in the elderly and associated with aortic stenosis and renal failure. The majority of cases present with anemia and cease bleeding spontaneously; however, 50% will rebleed in 5 years. Massive bleeding may occur in up to 15% of cases.
In the colon, angiodysplastic lesions are predominantly located in the cecum and ascending colon. Colonoscopy reveals red stellate lesions with a rim of pale mucosa. Angiographic features include early prolonged filling of the draining vein, clusters of small arteries, and a visible vascular tuft (Fig. 17-14). First-line treatment options include endoscopic or angiographic intervention. Bleeding refractory to these treatments requires a segmental colectomy, usually a right hemicolecctomy.

**FIGURE 17-14** Telangiectatic lesions (black arrows) characteristic of colonic angiodysplasia, seen on colonoscopy. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)

**Neoplasia.** Neoplasia is a rare cause of lower GI bleeding, accounting for only 2% to 9% of all hematochezia, but is significant due to the fairly high incidence of colorectal cancer in developed countries. Neoplasia-induced hemorrhage presents as chronic painless bleeding, usually associated with iron deficiency anemia, often from tumors of the right colon. Tumors of the left colon often present with obstructive symptoms but can also ulcerate to produce bright red bleeding (Fig. 17-15). Colonic polyps, especially those >1 cm in diameter, can bleed in 5% to 11% of patients and cause anemia in 3%
to 7% of patients (Fig. 17-16). Treatment for bleeding tumors is usually surgical, following diagnosis and staging with colonoscopy, biopsy, and appropriate imaging. Colon tumors are covered in more detail in Chapter 49.

FIGURE 17-15 Colonoscopic views of a large ulcerated neoplastic lesion. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)
Another common cause of lower GI bleeding is post-polypectomy bleeding, which can occur up to 2 weeks following polypectomy (Fig. 17-17). Risk of post-polypectomy bleeding is influenced by polyp size, inadequate electrocautery, comorbidity, bowel preparation, and experience of the endoscopist. Delayed post-polypectomy bleeding is more frequent in large polyps, right-sided polyps, and in patients on anticoagulation.
Anorectal Disease. Benign anorectal pathology can present as lower GI bleeding. History and physical examination can often confirm the diagnosis. Anal fissures cause pain with defecation and examination but rarely cause significant blood loss. Inspection of the anal margin is usually diagnostic and can be made painless following injection of local anesthetic. Bleeding from fissures usually stops spontaneously. Management includes the use of stool bulking agents, stool softeners, increased fluid intake, and topical nitroglycerin or diltiazem, which facilitate healing of the fissure by reducing sphincter spasm.

Hemorrhoids account for lower GI bleeding in 2% to 9% of patients. Fresh red blood is seen on the tissue paper, in the bowl, and around the stool. Bleeding is often painless and from internal hemorrhoids. Management includes stool bulking agents and increased dietary fiber with hydration. Surgical treatments include rubber band ligation, injection sclerotherapy, infrared coagulation, and hemorrhoidectomy.

More unusual anorectal causes of bleeding include solitary rectal ulcers and anorectal varices. Solitary rectal ulcers are believed to arise as a result of
local ischemia and rarely bleed. In contrast, anorectal varices occur in up to 18% of patients with portal hypertension and can cause severe bleeding.\footnote{105}

It is important to note that benign anorectal diseases such as anal fissures and hemorrhoids are common findings, and particularly in the elderly, other sources of proximal bleeding, especially tumors, should be excluded. Benign anorectal conditions are discussed further in Chapter 52.

Colitis

\textit{Inflammatory Bowel Disease.} Lower GI bleeding occurs in the majority of patients with ulcerative colitis and in up to one-third of patients with Crohn’s disease.\footnote{106} Most bleeding stops spontaneously, but 35% of patients will rebleed.\footnote{107} Both ulcerative colitis and Crohn’s are associated with abdominal pain and increased bowel movements. Both Crohn’s and ulcerative colitis are diagnosed on endoscopy and managed with 5-aminosalicylic acid (5-ASA) compounds, immunomodulatory agents, steroids, and antibiotics as needed (Fig. 17-18). Surgical therapy for ulcerative colitis is needed if the rare complication of toxic megacolon develops or in the event of refractory life-threatening hemorrhage. Surgery is avoided as much as possible in Crohn’s disease due to the natural relapsing and remitting nature of the disease and the tendency of the lesions to affect any region of the GI tract. Crohn’s disease and ulcerative colitis are discussed further in Chapters 45 and 46, respectively.
Infectious Colitis. Causes of infectious colitis that may cause bloody diarrhea include cytomegalovirus (CMV) colitis, *Escherichia coli*, *Shigella*, *Salmonella*, and *Campylobacter* infection. Patients with infectious colitis typically present with bloody diarrhea with positive stool cultures. CMV colitis typically affects the immunocompromised.

Patients with HIV are particularly at risk of GI bleeding, and due to the immune deficiency, are particularly at risk for opportunistic infections. Causes of colonic bleeding in HIV-positive patients include CMV, lymphoma, histoplasmosis, Kaposi sarcoma, and bacterial colitis, with an overall average mortality of 14%.\textsuperscript{108} Colonoscopy and biopsy confirm the diagnosis, and treatment should be commenced as appropriate.

**NSAID-Associated Lower GI Bleeding.** NSAIDs can also induce and exacerbate lower GI bleeding. NSAIDs can themselves induce mucosa damage and colonic inflammation, erosions, and ulcers. In addition, they can
exacerbate existing colitis and increase the tendency of pre-existing lesions such as polyps or angiodysplasia to bleed. NSAID-induced lesions appear as flat, irregularly-shaped erosions and ulcerations with otherwise normal mucosa.\textsuperscript{95}

**Radiation Proctitis.** Radiation therapy in the pelvic region is another cause of lower GI bleeding, producing a chronic radiation proctopathy due to the neovascularization resulting from radiation-induced endarteritis obliterans. Bleeding occurs in 4\% to 13\% of patients receiving radiation therapy for prostatic carcinoma.\textsuperscript{109} Patients typically present with bloody diarrhea, crampy pelvic pain, and tenesmus. Endoscopy reveals multiple telangiectasias on an otherwise pale mucosa, and can be coupled with APC for treatment (Fig. 17-19). Other treatment options include antidiarrheals and hydrocortisone enemas. Ablation with 4\% formalin solution may be considered for refractory bleeding.\textsuperscript{110}

![Colonoscopic view of radiation-induced proctitis](image)

**FIGURE 17-19** Colonoscopic view of radiation-induced proctitis, with the characteristic appearance of multiple telangiectasia on a background of otherwise pale mucosa. (Used with permission from Dr Nicola Simmonds, Luton and Dunstable Hospital, UK.)
**Ischemic Colitis.** Ischemic colitis, or mesenteric ischemia, results from a reduction in blood flow to the intestine due to either reduced blood pressure or vasoconstriction. Ischemic colitis occurs more frequently in the elderly and those with a history of cardiovascular disease. Other risk factors include recent abdominal vascular surgery, hypercoagulable states, and vasculitis. Patients on inotropes and vasoconstrictors are particularly prone to ischemic colitis due to splanchnic vasoconstriction. The splenic flexure of the colon and the rectosigmoid junction are vascular watershed areas and are especially susceptible to ischemia. Patients present with abdominal pain and bloody diarrhea. The diagnosis is suspected with the identification of a thickened bowel wall on CT, and confirmed on endoscopy showing bleeding, edematous mucosa with a demarcation between ischemic and normal bowel (Fig. 17-20). Ulcerations may appear on endoscopy in the later stages of disease progression. Despite the self-limiting nature of the disease in most patients, ischemic colitis is associated with a high morbidity and mortality.\(^{111}\) Conservative management is usually employed, with bowel rest, intravenous antibiotics, and cardiovascular support to normalize hemodynamics. In 15\% of patients, ischemia is followed by gangrene and perforation, requiring urgent laparotomy with resection of the ischemic bowel.\(^{112}\)

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**FIGURE 17-20** Ischemic colitis as viewed on colonoscopy, with evidence
OBSCURE LOWER GI BLEEDING

Bleeding persisting or recurring after negative esophagogastroscopy and colonoscopy occurs in approximately 5% of cases and is termed obscure bleeding, often the result of angiodysplastic lesions, Meckel diverticulae, Dieulafoy lesions, and small bowel neoplasms.\textsuperscript{113} Bleeding in these cases may be visible (termed obscure-overt bleeding) or only detected by the presence of guaiac-positive stools (obscure-occult bleeding). Further investigation in the form of capsule enteroscopy, deep enteroscopy, angiography, or red cell labeling is often necessary in these cases.

**Angiodysplasia.** Angiodysplasia is the most common cause of small bowel bleeding, accounting for up to 40% of cases in elderly patients and 10% of cases in younger patients. The jejunum is the most common site for these lesions. Small intestinal angiodysplasias often present with obscure or occult bleeding. Unlike colonic angiodysplasia, angiography is rarely helpful in small intestinal angiodysplasias. Capsule or deep enteroscopy are the investigative modalities of choice. Optimal management involves segmental resection of the affected small bowel with on-table endoscopy as needed. However, it is important to note that a significant number of patients may spontaneously stop bleeding.\textsuperscript{114}

**Meckel and Other Small Intestinal Diverticulae.** A Meckel diverticulum is the incomplete obliteration of the remnant embryonic vitelline duct that connects the yolk sac and fetal gut. Meckel diverticulum are true diverticula, occur in 2% of the population, are usually located within 100 cm of the ileocecal valve, and range from 1 to 10 cm in length (\textbf{Fig. 17-21}).\textsuperscript{115} Up to 60% of Meckel diverticulae contain heterotopic mucosa, usually of gastric or pancreatic origin. Hemorrhage is a common complication of a Meckel diverticulum, occurring in 38% of adults and 31% of children, and results from ulceration of the normal mucosa adjacent to the acid-producing heterotopic mucosa.\textsuperscript{116} Radionuclide scans may assist in the diagnosis of Meckel diverticulum, but are less accurate in adults than in children. Cimetiidine slows the release of the pertechnate into the lumen and increases
the sensitivity of a Meckel scan.\textsuperscript{117} Laparoscopy may be used for the diagnosis as well as the treatment of Meckel diverticulum. Operative management hinges on removal of the Meckel diverticulum and resection of adjacent affected bowel.

![Meckel diverticulum seen intraoperatively. The Meckel diverticulum (black arrow) can be seen on the antimesenteric border of the ileum.](image)

**FIGURE 17-21** Meckel diverticulum seen intraoperatively. The Meckel diverticulum (black arrow) can be seen on the antimesenteric border of the ileum.

The incidence of non-Meckelian intestinal diverticulosis is low, ranging from 0.06\% to 4.6\% on autopsy studies.\textsuperscript{118} They are more common in the elderly but may present at any age. Small bowel diverticulae, like colonic diverticulae, are pseudodiverticulae involving only mucosa and submucosa. Most small intestinal diverticulae are found in the jejunum, where vasa rectae are more frequent. Upper GI contrast series or CT scans may reveal small bowel diverticulae but are not sensitive investigations. Enteroclysis can increase sensitivity for small diverticulae but are not a cost-effective first-line
study. The incidence of bleeding from jejunal diverticulosis ranges from 5% to 33%. Enteroscopy (particularly deep enteroscopy) is suitable for diagnosis of diverticulae complicated by bleeding, inflammation, or obstruction, but laparotomy remains the gold standard for diagnosis and management, particularly in the unstable patient. Operative management involves resection of the affected segment of small bowel with a primary end-to-end anastomosis. Rarely, a large proportion of the bowel is involved (panjejunioileal diverticulosis), and conservative management may be trialed to avoid the need for massive small bowel resection. Selective mesenteric angiography and embolization may assist in the control of hemorrhage in these cases.

**Neoplasia.** Although small bowel tumors account for only 5% of all GI tumors, they are the second most common cause of small intestinal bleeding. Patients present either with melena or occult bleeding. Leiomyomas and leiomyosarcomas are the tumors which most commonly bleed from tumor necrosis and mucosal ulceration. These are highly vascular tumors and hence angiography has an 86% rate of detection for these lesions. Other small intestine tumors include adenocarcinomas, carcinoids and lymphomas. Tumors can be diagnosed by enteroscopy, small bowel contrast series, or CT (Fig. 17-22). Treatment is surgical resection of the tumor.
FIGURE 17-22 CT image of an ileal adenocarcinoma, obvious as a mass in the left mid-abdomen.

REFERENCES


LESIONS OF THE OMENTUM, MESENTERY, AND RETROPERITONEUM

Tara A. Russell • Fritz C. Eilber

MESENTERY

The entire gastrointestinal tract is derived from a common dorsal mesentery. During development, as the mesentery fuses with the retroperitoneum, the remaining segments become the small bowel mesentery, transverse mesocolon, and sigmoid mesocolon. These mesenteries serve as the primary pathways to and from the bowel for arterial, venous, lymphatic, and neural structures.

The small bowel mesentery originates as the root of the mesentery, located at the fourth part of the duodenum and posterior border of the pancreas. It courses along the medial border of the jejunum and ileum in a fan-like projection. The transverse mesocolon connects the transverse colon to the retroperitoneum, and the sigmoid mesocolon connects the sigmoid flexure to the inferior retroperitoneum and pelvis.
Acute Mesenteric Lymphadenitis

Acute mesenteric lymphadenitis (AML) is the marked focal inflammation of mesenteric lymph nodes and has been associated with viral illness and other infectious processes. AML most commonly occurs in children, with an equal distribution in males and females. The most common presenting symptoms are abdominal pain, mild fever, nausea, and occasionally vomiting. Both laboratory and systemic symptoms are less severe in comparison to those seen with acute appendicitis.

Given the young age at presentation, most children undergo ultrasound rather than computed tomography (CT) for diagnosis. Diagnostic criteria by either ultrasound or CT include clusters of enlarged (>5-8 mm) hypervascular mesenteric lymph nodes with a normal appendix. While imaging findings are often suggestive, true diagnosis is often made at the time of negative appendectomy, when mesenteric lymphadenopathy is noted.

When AML is suspected, one can proceed with supportive care, as the disease is self-limiting and typically resolves without invasive measures. Given that the inciting agent is typically viral, there is no indication for antimicrobial agents.

Mesenteric Panniculitis/Sclerosing Mesenteritis

Mesenteric panniculitis was first described in 1927 by Jura as an infiltration of plasma and polymorphonucleated cells into the mesentery. The condition, now more vigorously investigated, has many names throughout the literature including sclerosing mesenteritis, retractile mesenteritis, and mesenteric lipodystrophy. The disease process of marked mesenteric inflammation and fibrosis more commonly affects the small bowel mesentery and can be asymptomatic or present as diffuse, nonspecific abdominal pain. Most cases present in the sixth decade, with a slight male predominance. The etiology is not well understood and has been related to various sources including autoimmune, infectious, ischemic, and traumatic causes. In one study, 35% of patients with sclerosing mesenteritis were noted to have a history of abdominal surgery, and therefore, surgical trauma may be a predisposing factor.

The inflammation and fibrosis originate at the root of the mesentery and
proceed to involve varying amounts of the mesentery. Histologically, the disease is classified into 3 stages, based on the relative proportions of fatty and fibrotic changes. Mesenteric lipodystrophy has fatty predominance and is characterized by replacement of mesenteric fat by a layer of foamy macrophages. Mesenteric panniculitis, composed of both fatty and fibrotic changes, is marked by plasma and polymorphonuclear leukocytes as well as foreign body giant cells and foamy macrophages. Finally, sclerosing mesenteritis, or retractile mesenteritis, is marked by fibrotic changes with collagen deposition, fibrosis, and inflammations.

This process is most frequently diagnosed by CT scan. Findings often include an adiposidic mass, which often encases the mesenteric vessels and displaces but does not directly invade the bowel (Fig. 18-1). Additional imaging with magnetic resonance imaging (MRI) may help with diagnosis, but this will not ultimately change management. Positron emission tomography (PET) imaging may be helpful in distinguishing mesenteric panniculitis from lymphoma or metastatic disease, as mesenteric panniculitis will have minimal PET avidity. While the majority of these cases can be diagnosed by imaging findings, if there is suspicion for malignancy or if surgical intervention is undertaken due to symptoms or obstruction, biopsy is warranted.


Mesenteric panniculitis is a self-limiting disease, and therefore, if it is
asymptomatic, it requires no intervention. Alternatively, for the >20% of patients who do report a debilitating course due to chronic abdominal pain, intervention is primarily medical and focuses on decreasing inflammation and fibrosis with a variety of therapeutic agents including corticosteroids, cyclophosphamide, or colchicine.\textsuperscript{7,8,10} For patients who present with symptoms of obstruction and are refractory to medical management, surgical intervention may be warranted and should focus on relieving the area of obstruction with segmental resection of the involved mesentery and potentially segmental small bowel resection. If a patient does require surgical management, this should be followed by medical interventions, because surgery alone does not address the underlying problem.

**Mesenteric Cysts**

Although the majority of mesenteric cysts are congenital, only 60% present during childhood, with up to 40% presenting during adulthood, most commonly in the fourth decade.\textsuperscript{13-15} The overall incidence is estimated to be <1/100,000, and etiology varies from failure of mesenteric fusion to lymphatic malformation to trauma.\textsuperscript{10} The majority of mesenteric cysts are asymptomatic, but patients can present with either a mobile abdominal mass or pain.\textsuperscript{16} Abdominal pain typically arises secondary to rupture, torsion, or mass effect. On physical exam, palpable masses are frequently mobile in a single lateral direction (left to right or right to left), known as the Tillaux sign, and are not freely mobile, as is seen with omental cysts.

Ultrasound or CT is adequate for evaluating cystic lesions and delineating any solid components or septations.\textsuperscript{14,15} The majority of lesions are located within the small bowel mesentery, are unilocular, and do not have a solid component. Identification of a solid component should raise suspicion for malignancy, which only occurs in approximately 3% of mesenteric cystic masses, and is typically sarcoma or rarely adenocarcinoma.\textsuperscript{15}

More than 50% of the cystic mesenteric masses are lymphangiomas.\textsuperscript{11} The majority of lymphangiomas present within the head, neck, or axilla, whereas small bowel mesenteric lymphangiomas account for <1% of all cases.\textsuperscript{17} Lymphangiomas are classically solitary masses that develop due to congenital malformation of the lymphatic vessels, causing failure of the lymphatic channels to drain in the lymphatic system.\textsuperscript{17}
Treatment of any mesenteric cyst requires surgical excision if the patient is symptomatic or malignancy has not been ruled out, with preference for a laparoscopic approach. Cysts should be excised in total because enucleation, marsupialization, internal or external aspirations, and drainage are associated with a high risk of recurrence.\textsuperscript{10,15}

**Mesenteric Tumors**

**MESENTERIC MESOTHELIOMA**

Mesothelioma is the uncontrolled proliferation of mesothelial cells found in the serosal lining of the pleura, pericardium, peritoneal cavity, and mesentery.\textsuperscript{9} Mesenteric mesothelioma accounts for 25\% of all mesotheliomas and 6\% to 10\% of malignant mesotheliomas.\textsuperscript{18,19} Among malignant disease, diffuse malignant peritoneal mesothelioma is the second most common site, with the most common site being pleural.\textsuperscript{19,20} Malignant mesotheliomas can be classified as epithelioid, sarcomatoid, or mixed, with epithelioid type being the most common.

Mesothelioma was poorly understood until its association with asbestos was reported by Wagner in 1960.\textsuperscript{21} The incidence of all mesothelioma, including mesenteric, has been rising since 1970, with the rate in the United States continuing to rise through the 1990s and plateauing shortly thereafter.\textsuperscript{19} The Surveillance, Epidemiology, and End Results database estimates that approximately 250 new cases of mesenteric mesothelioma are diagnosed annually.\textsuperscript{19,22} Among all mesothelioma, mesenteric primaries account for 11\% of diagnoses in men and 45\% of all diagnoses in women.\textsuperscript{23} This sex disparity has been debated in the literature, with the predominate theory indicating that the higher rate of female mesenteric primaries is due to the association of mesenteric mesothelioma with nonoccupation exposures, which often result in a higher dose and longer duration of exposure.\textsuperscript{22,23}

Malignant mesenteric mesothelioma typically presents with abdominal pain and increased abdominal distention secondary to accumulation of both tumor and ascites\textsuperscript{19} (Fig. 18-2). CT imaging demonstrates diffuse involvement of the peritoneal surfaces, innumerable nodules within both the abdomen and pelvis, and ascites.\textsuperscript{24,25} Local invasion into the bowel and solid viscera can occur in advanced disease, and metastases are usually to regional
lymph nodes. Diagnosis requires either a CT-guided or laparoscopic biopsy, as diagnostic paracentesis has repeatedly been shown to have low diagnostic yield.  

**FIGURE 18-2** Diffuse malignant peritoneal mesothelioma. Macroscopically, this disease is characterized by thousands of whitish tumor nodules of variable size and consistency that may coalesce to form plaques or masses or layer out evenly to cover the entire peritoneal surface. (Reproduced with permission from Munkholm-Larsen S, Cao CQ, Yan TD: Malignant peritoneal mesothelioma, *World J Gastrointest Surg* 2009 Nov 30;1(1):38-48.)

The treatment and management of malignant mesenteric mesothelioma are not well defined. Historically, this diagnosis is associated with very poor survival, frequently less than 1 year, secondary to progression, solid organ invasion, bowel obstruction, and malnutrition. Multiple therapies have been attempted in this rare disease including surgical debulking and intraperitoneal and intravenous chemotherapy. Although there is no consensus or level 1 evidence due to the lack of randomized controlled trials for this disease, large retrospective reviews have evaluated the impact of both cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) and advocate for a combined approach.  

Cytoreductive surgery includes
removal of all visible tumor, peritoneectomy, greater omentectomy with splenectomy, lesser omentectomy with cholecystectomy, and pelvic peritoneectomy with rectosigmoid colonic resection. Completeness of the surgery is graded by the size of the largest remnant nodules (0 = no residual tumor, \(1 = < 2.5 \text{ mm}, 2 = \text{ between } 2.5 \text{ mm and } 2.5 \text{ cm}, 3 = > 2.5 \text{ cm}\)) and is the factor most strongly associated with posttreatment survival. Intraperitoneal chemotherapy regimens vary, but most commonly include cisplatin and/or doxorubicin and can be given intraoperatively at the time of surgery or at an interval after cytoreductive surgery. Studies evaluating the combined approach of cytoreductive surgery with HIPEC suggest there is a significant survival advantage, with one of the largest reviews reporting 81%, 60%, and 47% survival rates at 1, 3, and 5 years, respectively.\(^{27}\) Therefore, in the setting of a diagnosis of mesenteric mesothelioma, referral to a specialized center is highly recommended.

**DESMOIDS**

Desmoid tumors were first named by Muller in 1938.\(^{29}\) Microscopically, they are composed of collagen, fibroblasts, and bundles of spindle-shaped cells, often with poorly circumscribed margins and no distinguishable capsule.\(^{9,29,30}\) They are of mesenchymal origin and therefore can arise anywhere in the body. The most common sites include extremities, anterior abdominal wall, and mesentery. Within the United States, the annual incidence is 2.4 to 4.3 per 100,000.\(^{11}\) Mesenteric desmoids account for only 8% of all desmoids tumors and most commonly develop in patients with familial adenomatous polyposis (FAP).\(^{6,9,31}\)

FAP, which is classically associated with colonic polyposis and increased risk for colonic adenocarcinoma, has multiple extracolonic manifestations, including desmoid tumors. Patients with FAP have a 20% lifetime risk of desmoid tumor formation, of which 80% are intra-abdominal, 10% to 15% occur within the abdominal wall, and 5% are extra-abdominal.\(^{29}\) Desmoids associated with FAP are considered to be more aggressive and have a higher risk of mortality to due to local invasion, unlike desmoids of other anatomic locations that have no associated mortality.\(^{6}\)

Although desmoid tumors can arise within a previous scar or incision, they may also occur sporadically. Mesenteric desmoids are more frequent after
abdominal surgery and, in FAP patients, after prophylactic colectomy.\textsuperscript{29} Desmoids are locally invasive tumors that may invade surrounding structures or cause mass effect but do not metastasize. Therefore, clinical presentation is often due to a palpable abdominal mass or secondary mass effect and compression of intra-abdominal structures including ureters, pelvic vessels, or the bowel.\textsuperscript{29}

Diagnosis is made by either CT or MRI, and need for intervention is based primarily on symptoms. Interestingly, the natural history of intra-abdominal desmoids tumors shows a unique pattern, in which approximately 10\% resolve spontaneously, 30\% undergo cycles of progression and resolution, 50\% stabilize, and 10\% progress rapidly.\textsuperscript{32} Due to this indeterminate course, many recommend serial imaging with CT to characterize an individual tumor’s propensity for growth.\textsuperscript{29,32,33}

The treatment of desmoid tumors is best handled in the context of a multidisciplinary sarcoma program because there are a number of potential interventions, including surgical, medical, and radiation therapy. In particular, for small intra-abdominal desmoids that are slow growing and/or not in close proximity to vital structures, there is no clear indication for intervention, only serial monitoring with CT or intervention for symptoms alone.\textsuperscript{29,32} For large masses or for those causing compressive effect, a multimodal approach is recommended.\textsuperscript{30,32,34,35} Surgical resection requires complete en bloc resection of the mass. Because desmoids often have ill-defined borders, positive margins are not uncommon.\textsuperscript{36,37} Unlike most sarcomas, re-resection of a positive margin or performing an extensive multiorgan resection for a desmoid is not done. Because mesenteric desmoids have a high recurrence risk and the required operation for complete resection is often highly morbid, medical therapies are now considered the treatment of choice.\textsuperscript{9,29,30,32} A number of systemic treatment options are available, all of which have variable success rates and are best handled by an experienced sarcoma medical oncologist. The potentially effective systemic treatment options vary greatly in toxicity and include nontoxic agents (eg, nonsteroidal anti-inflammatory drugs, tamoxifen, hydroxyurea), marginally toxic treatments (eg, methotrexate and vinblastine), and more toxic traditional chemotherapy (eg, doxorubicin and dacarbazine).\textsuperscript{30,32,38} There has been recent success with the newer targeted therapies, and currently, the Desmoid Tumor Research Foundation and the National Cancer Institute are running a
national trial using sorafenib based on recent success with this agent. Although radiation therapy is often used in the treatment of extremity desmoids, it is generally avoided for intra-abdominal or mesenteric desmoids.

**METASTATIC DISEASE**

Primary disease of the mesentery is rare, with the 2 most common forms discussed above. However, both systemic and metastatic disease can present within the mesentery, either due to symptoms of an abdominal mass or pain or as incidental imaging findings.

Lymphoma is the most common solid neoplasm identified within the mesentery. While very few patients present with symptoms of a palpable mass, bulky adenopathy is frequently noted. On CT imaging, mesenteric lymphoma presents as an agglomeration of homogenously enhancing lymphadenopathy that typically does not invade or obstruct the mesenteric vessels or the bowel. The most common form of lymphoma to present with mesenteric lymphadenopathy is non-Hodgkin lymphoma. Treatment is primarily nonsurgical, and therefore, these cases should be referred to a medical oncologist.

Metastases from other primary cancers are also common within the mesentery. Metastatic spread can occur through direct extension, intraperitoneal seeding, or hematogenous or lymphatic spread. The most common primary tumors resulting in mesenteric metastases include ovarian, gastrointestinal, melanoma, breast, pancreatic, and bladder tumors. Diagnosis typically includes additional imaging to identify a primary site and may require image-guided or laparoscopic biopsy for tissue diagnosis.

Furthermore, gastrointestinal primaries, including gastrointestinal stromal tumors (GISTs) and carcinoid tumors, may initially present as mesenteric disease due to local extension or invasion. These tumors should be treated as gastrointestinal primary tumors, and therefore, further discussion of diagnosis and management can be found in other chapters.

**OMENTUM**

The greater omentum is a thin fibrofatty apron composed of 2 fused bilayers of peritoneum, with one bilayer originating along the greater curvature of the
stomach and a second along the transverse colon. These 2 bilayers fuse and then extend inferiorly and anteriorly over the small bowel and into the pelvis and laterally to the pylorus and gastroplenic ligament. The lesser omentum is a smaller bilayer of peritoneum that extends from the liver to the lesser curvature of the stomach, including the hepatoduodenal and hepatogastric ligaments.

The omentum has many theoretic functions and was coined the “abdominal policeman” by the British surgeon Rutherford Morison due to its ability to wall off areas of infection and limit its spread. The propensity for this policing arises due to the high concentration of tissue factor within the omentum, which assists with activation of coagulation and fibrosis at the sites of inflammation, infection, ischemia, and trauma.

**Omental Torsion and Infarction**

Omental torsion and infarction were first described by Eitel in 1899 and arise when a pedicle of omentum twists along its axis, compromising the vascular supply. Such torsion then progresses from vascular congestion and thrombosis to arterial occlusion and ultimately necrosis of the omentum, with associated extravasation of serosanguinous ascites. Cases of omental torsion are rare. The majority of cases occur in male adults, typically in the fourth to fifth decade.

Given the anatomic pattern of the omental sheet, torsions typically occur in the right or left lower quadrant and therefore may mimic the pain of other intra-abdominal pathologies including appendicitis, diverticulitis, ruptured ovarian cysts, and rarely cholecystitis. Clinical history often reveals localized pain without the presence of gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Physical exam may reveal diffuse abdominal tenderness, mild peritoneal signs, and in some cases, a tender palpable mass. Approximately 50% of patients will have a low-grade fever and mild leukocytosis.

Torsion can be either primary or secondary. Primary omental torsions arise due to anatomic abnormalities including tongue-like projections, accessory omentum, or anomalous vascular supply, whereas secondary torsions are associated with hernias, cysts, scaring, tumors, or foci of intra-abdominal inflammation. Some reports have demonstrated an
increased risk associated with obesity, such that in one study >70% of patients with omental torsion were also obese. This association is attributed to the increased density and thickening of the omentum acting as a lead point.

Additionally, infarction of the omentum can occur without preceding torsion. Omental infarction can be either idiopathic segmental infarction or secondary infarction. Secondary infarction occurs in the setting of systemic disease including vasculitis, hypercoagulability, or thrombi. The presentation of isolated infarction or infarction secondary to torsion is similar.

Appropriate radiographic evaluation includes an abdominal and pelvic CT scan with intravenous contrast, which often demonstrates a localized inflammatory mass, with a whirl sign or concentric linear stranding. Fat stranding in the area will be disproportionate to any adjacent bowel wall thickening, indicative of a pathologic process centered within the omentum rather than the bowel.

If radiographic studies can conclusively exclude any bowel involvement, these patients can be observed clinically and managed supportively. Alternatively, if there is any clinical instability, pain does not improve within 24 to 48 hours, or other potential etiologies cannot be excluded (appendicitis), laparoscopic exploration with possible resection of the infarcted tissue should be performed.

**Omental Cysts**

Omental cysts, which arise due to peritoneal inclusions or lymphatic degeneration, are a rare condition, most commonly diagnosed in children. On exam, these masses are freely mobile due to laxity of the omentum. Like other cystic masses, these can be imaged by ultrasound to exclude any solid component and are ultimately treated with simple excision or marsupialization. Given the small risk of malignancy, these specimens should always be carefully reviewed with a pathologist.

**Omental Tumors**

Primary omental tumors are exceedingly rare, with the majority of the literature composed of case reports and small series. Given that the omentum
is composed of various tissues, the origin of an omental mass can be very
diverse, with tumors of mesenchymal origin being the most common. Benign
tumors include lipomas, myxomas, leiomyomas, and desmoids. Malignant
tumors include leiomyosarcoma, liposarcoma, and mesothelioma.

The omentum is also a site for distant metastatic disease, with ovarian
cancer being the most common primary. Other primaries that can metastasize
to the omentum include melanoma, uterine, renal cell, pancreatic, and
gastrointestinal cancers. Metastatic disease can present focally or in the
form of omental caking, which is characterized by the diffuse thickening of
the omentum and replacement of fat with metastatic islands.

Of note, there are some infectious etiologies that may present with
omental involvement, in particular tuberculous peritonitis, actinomycosis,
and coccidiomycosis. The majority of these infectious etiologies are
associated with additional systemic symptoms, and therefore, only rarely is
an omental mass or thickening the first sign of disease.

While most masses of the omentum are diagnosed incidentally, patients
can present with a focal mass or abdominal pain. Diagnostic workup includes
CT imaging of the abdomen and pelvis, with some studies indicating
increased diagnostic accuracy with the addition of CT angiography to
delineate the presence of feeding vessels or to determine hypervascularity
(favoring a malignant process). If there is diffuse involvement of the
omentum, which is more suggestive of metastatic disease, one should
thoroughly evaluate for a primary tumor.

Given the wide differential upon identification of omental thickening or
mass, further diagnostic workup is warranted. While open or laparoscopic
biopsy has frequently been used for tissue diagnosis, multiple studies have
demonstrated high sensitivity and specificity with large core needle biopsies
of omental lesions, ranging from 89% to 93% and 86% to 100%,
respectively. Therefore, to rule out metastatic disease, it is recommended to
initially proceed with ultrasound or CT-guided core needle biopsy for tissue
diagnosis. Surgical biopsies should be only undertaken if an image-guided
core needle biopsy is not diagnostic because surgery will only delay systemic
treatment.

RETROPERITONEUM
The retroperitoneum is defined as the space between the posterior aspect of the peritoneum and posterior abdominal wall. It is bounded by the diaphragm superiorly, spinal column and iliopsoas posteriorly, and levator ani muscles inferiorly. Within the trauma literature, the retroperitoneum is divided into 3 zones: zone 1 = central retroperitoneum, defined as the space between the renal hila containing the abdominal aorta, inferior vena cava, celiac axis, superior mesenteric artery, and proximal renal vasculature; zone 2 = lateral retroperitoneum, including all structures lateral to the renal hilum including the kidneys, adrenals, and proximal genitourinary tract; and zone 3 = pelvic retroperitoneum, bound superiorly by the bifurcation of the abdominal aorta and including the iliac vessels and their branches, rectum, and distal genitourinary tract.50

**Retroperitoneal Hemorrhage**

Retroperitoneal hemorrhage can occur spontaneously or secondary to iatrogenic injury or trauma. The etiology of secondary retroperitoneal hematomas varies significantly and includes complications of femoral artery catheterization; pelvic or lumbar trauma; ruptured abdominal aortic, iliac, renal, or mesenteric aneurysms; or bleeding from any retroperitoneal structure (pancreas, adrenal glands, or kidneys).51,52

The presentation of retroperitoneal hematoma varies, but outside of traumatic injury, it is typically marked by clinical signs of hemorrhage, with relative hypotension and mild tachycardia. Some patients report back, lower abdominal, flank, or groin discomfort or swelling, and late signs, due to mass effect, may include neuropathy of the femoral nerve or iliopsoas muscle spasm.53-55 In addition, patients may have cutaneous findings, including Grey-Turner sign, flank bruising, or Cullen sign, superficial edema, and bruising of the periumbilical tissue.

Spontaneous retroperitoneal bleeding has an incidence of 0.6% to 6.6% and most commonly occurs in the elderly, likely secondary to increased use of antiplatelet agents and anticoagulants in this population.51,53 Spontaneous bleeds can arise due to underlying coagulopathy (factor IX or X deficiency, von Willebrand disease, or antiphospholipid syndrome), spontaneous hemorrhage (adrenal cysts), or vascular rupture. The pathophysiology of these bleeds is unclear, but it has been hypothesized that atherosclerosis and
vasculopathy affecting the small vessels of the retroperitoneum lead to increased friability and ultimate rupture.\textsuperscript{51} It is clearly documented that all forms of anticoagulant and antiplatelet drugs increase the risk of hemorrhage, with unfractionated heparin having an elevated risk, estimated at 2 to 5 times that of warfarin.\textsuperscript{51,53}

Iatrogenic retroperitoneal hemorrhage secondary to percutaneous vascular access was first described in 1963 in the setting of translumbar aortography.\textsuperscript{51} Retroperitoneal bleeding occurring as a complication of femoral catheterization is one of the most common causes of secondary bleeding and arises from inadvertent puncture of the posterior wall of the femoral or iliac artery during cannulation. The incidence after cardiac catheterization is estimated at 0.15%, and the incidence after femoral artery catheterization for all purposes is 0.5%; yet some series report an incidence as high as 5% to 6%.\textsuperscript{51,56-58} The range in incidence is likely due to differences in technique, equipment, and the number of punctures; use of vascular closure devices; concomitant use of anticoagulants and antiplatelet agents; and patient-specific factors.

Traumatic retroperitoneal bleeding typically arises in the setting of blunt pelvic trauma, although it may also occur with penetrating injuries. Blunt trauma, resulting in pelvic fracture, has a high risk of retroperitoneal hemorrhage due to the close anatomic proximity of the pelvis with the internal and external iliac arteries and their respective branches. Mortality secondary to pelvic fractures and retroperitoneal hemorrhage has improved with new techniques in resuscitation and endovascular therapy but still remains high (approximately 20%).\textsuperscript{59} The majority of bleeding occurs due to lesions within the venous system, specifically the presacral and prevesical veins, yet those bleeds resulting in hemodynamic instability are more likely arterial in nature.\textsuperscript{59} External pelvic stabilization has been shown to slow venous bleeding secondary to pelvic fractures in the setting of trauma and can be used as an adjunct while initiating hemostatic interventions. Surgical intervention is mandated in all zone 1 and penetrating injuries to the retroperitoneum to assess and control any potential vascular bleeding. Conversely zone 2 and 3 bleeds after blunt trauma should only be explored in the setting of pulsatile bleeding or rapid expansion.\textsuperscript{60}

In addition to the clinical signs discussed previously, retroperitoneal hemorrhage or hematoma is typically diagnosed with imaging. While
ultrasound has been applied for evaluation of intra-abdominal fluid, it is not specific or sensitive for retroperitoneal bleeding.\textsuperscript{51,61,62} Therefore, CT, preferably with intravenous contrast or angiography, is recommended.\textsuperscript{51,61} On CT, retroperitoneal hematomas appear as abnormal soft tissue densities that compress adjacent normal structures. Contrast-enhanced imaging has the added ability to demonstrate extravasation of contrast and a layering effect within the hematoma. The further addition of angiography can help to isolate a feeding vessel, which is pertinent for any endovascular intervention.

In the setting of spontaneous bleeds attributable to anticoagulant therapy or coagulopathy, conservative management with intensive monitoring, fluid resuscitation, and correction of coagulopathy is advocated.\textsuperscript{51,53} Surgical intervention with plans for evacuation of the hematoma risks alleviating any potential for tamponade and therefore is not advocated.\textsuperscript{58}

There is growing evidence that, in cases with expanding hematomas either spontaneous or iatrogenic in origin, endovascular techniques with intra-arterial embolization or stent grafts can stop bleeding, without the associated risk of disturbing tamponade.\textsuperscript{51,58} Recommendations for endovascular embolization advocate intervention for hemodynamic instability despite 4 or more units of blood transfusion within 48 hours or whenever clear arterial extravasation is identified.\textsuperscript{63} As previously stated, surgical intervention for retroperitoneal hematomas is typically avoided unless there is severe hemodynamic instability, abdominal compartment syndrome, or femoral nerve compression. In this setting, the goals of open surgery would include control of any site of active bleeding, removal of the hematoma, and potentially packing the retroperitoneum for 24 to 48 hours.

**Retroperitoneal Abscess**

Retroperitoneal abscesses arise secondary to an infection within an organ contained within or abutting the retroperitoneum. Common primary sources include diverticulitis, retrocecal appendicitis, Crohn disease, osteomyelitis, renal lithiasis, pancreatitis, or biliary tract disease.\textsuperscript{64} Within the retroperitoneum, there are no anatomic boundaries that limit the spread of infection, except Gerota fascia surrounding the kidney; therefore, infections are often large and can be difficult to manage. They are most common in adults age 30 to 60 years, with no sex predominance.\textsuperscript{10} Patients are typically
ill appearing and present with pain localized to the lower abdomen and flank, fever, nausea, vomiting, or changes in bowel habit, and potentially sepsis. In some patients, referred pain is present in the hips and lower extremities. Physical exam typically reveals abdominal tenderness, a palpable mass in some patients, and a positive psoas sign.

Diagnosis is made with abdominal CT scan, with a reported sensitivity and specificity ranging from 90% to 100% in multiple series. Abscesses anterior to the pararenal space are often secondary to the retroperitoneal gastrointestinal organs, whereas the perirenal and posterior pararenal space abscesses are more likely secondary to kidney disease.

Management of retroperitoneal abscesses relies heavily on source control, drainage, and intravenous antibiotics. Cultures should be taken at the time of drainage to determine the appropriate directed antimicrobial therapy. Proteus, Escherichia coli, Bacteroides, and other gram-negative bacilli species are the most common given the proximity of the gastrointestinal tract, but other species, including gram-positive cocci, anaerobes, fungi (Candida), and tuberculous abscesses, have also been identified. Image-guided drainage is typically preferred over surgical interventions, as this provides a minimally invasive mechanism for decompression and continuous drainage without the added risk of surgery or dissemination due to violation of the retroperitoneum. Multiple case series have demonstrated high rates of success with percutaneous drainage and antibiotics alone, ranging from 45% to 100%. In the event of failure to improve with conservative management or prolonged hemodynamic instability, surgical intervention is warranted. Overall mortality associated with retroperitoneal abscesses is high, estimated at 15% to 25%.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis was first described by a French urologist Albarran in 1905 but was not recognized as a disease process until Ormond published the clinical course in 1948. Retroperitoneal fibrosis is characterized by chronic inflammation and fibrosis entrapping the ureters, abdominal aorta, and other abdominal organs. The characteristic inflammation and fibrosis typically begin around the abdominal aorta and extend laterally to involve the ureters. The disease is classified as either idiopathic or secondary.
Idiopathic retroperitoneal fibrosis has a reported incidence of 1.0 to 1.4 per 100,000, with a 2:1 male predominance. Among all cases of retroperitoneal fibrosis, two-thirds are idiopathic, with no clear inciting agent or process. Conversely, secondary retroperitoneal fibrosis occurs as an inflammatory reaction of chronic fibrosis in response to an inciting medication or inflammatory or malignant process (Table 18-1). The most common etiology is medications, with the greatest offenders being methysergide (semisynthetic ergot alkaloid used to treat migraines), β-blockers, hydralazine, α-methyldopa, and entacapone. Fibrosis occurring in the setting of malignant disease typically arises as a secondary desmoplastic reaction to retroperitoneal metastases or primary tumors (most commonly lymphoma). In addition, secondary retroperitoneal fibrosis has been associated with aortic aneurysm, pancreatitis, histoplasmosis, tuberculosis, actinomycosis, stromal and carcinoid tumors, and autoimmune disorders.

**TABLE 18-1: MAJOR CAUSES OF SECONDARY RETROPERITONEAL FIBROSIS**

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</tr>
<tr>
<td>Methysergide, pergolide, bromocriptine, ergotamine, methyldopa, hydralazine, analgesics, β-blockers</td>
</tr>
<tr>
<td>Malignant diseases</td>
</tr>
<tr>
<td>Carcinoid, Hodgkin and non-Hodgkin lymphomas, sarcomas, carcinomas of the colon, prostate, breast, stomach</td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Tuberculosis, histoplasmosis, actinomycosis</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Testicular seminoma, colon carcinoma, pancreatic carcinoma</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Lymphadenectomy, colectomy, hysterectomy, aortic aneurysmectomy</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Histiocytoses, Erdheim-Chester disease, amyloidosis, trauma, barium enema</td>
</tr>
</tbody>
</table>

Retroperitoneal fibrosis typically begins just caudal to the renal arteries.
and gradually expands, encasing the ureters, inferior vena cava, abdominal aorta, mesenteric vessels, and sympathetic nerves. Macroscopically, this fibrosis appears as white, hard, sclerotic plaques. Microscopically, it is characterized by progressive infiltration of inflammatory cells, which are later replaced with collagen-synthesizing fibroblasts. Multiple mechanisms have been hypothesized, with the dominant being that of an inflammatory reaction to oxidized low-density lipoproteins found within the atherosclerotic plaques.\textsuperscript{71,73}

Patients typically present with both localized and systemic symptoms. Localized symptoms arise secondary to mass effect or local invasion and include back, flank, or abdominal pain and lower extremity edema (secondary to either compression of the lymphatics or deep vein thrombosis). Systemic symptoms typically manifest as fatigue, low-grade fevers, nausea, anorexia, weight loss, or neuralgias. Eighty to 100\% of cases are associated with ureteral obstruction; therefore, urinary complaints are also common.\textsuperscript{71,72}

The diagnosis of retroperitoneal fibrosis has historically been made with intravenous urography, demonstrating the triad of medial deviation and extrinsic compression of the ureters and hydronephrosis. Yet, while this triad is useful in characterizing the ureteral involvement of the disorder, these findings may also be secondary to ureteral tumors, inflammatory processes, or adenopathy and are therefore not specific. The current recommendations for diagnosis include CT with intravenous contrast or MRI.\textsuperscript{72-74} CT findings demonstrate an accumulation of periaortic soft tissue that encases the distal aorta below the renal arteries. To confirm the diagnosis of retroperitoneal fibrosis and rule out a retroperitoneal malignancy, a CT-guided biopsy should be completed.\textsuperscript{10,74,75} In addition to imaging, laboratory tests will likely demonstrate an elevated erythrocyte sedimentation rate and C-reactive protein, which can both assist in diagnosis and be used for disease monitoring.\textsuperscript{71,73}

The management of retroperitoneal fibrosis requires a combined medical and surgical approach (Fig. 18-3). Corticosteroids are the mainstay of medical management and can lead to either stabilization or regression of fibrosis; surgical intervention is then only warranted in rare cases and usually due to compression and obstruction of the ureters or vascular structures. For patients unresponsive to corticosteroids, both azathioprine and cyclosporine have been demonstrated to induce remission or regression of disease. In
addition, there are anecdotal reports of tamoxifen, colchicine, methotrexate, and mycophenolate being effective in disease stabilization or regression. Overall long-term prognosis is good, with 5-year survival ranging from 90% to 100%.

FIGURE 18-3 Proposed algorithm for the management of retroperitoneal fibrosis. (Reproduced with permission from Vaglio A, Salvarani C, Buzio C: Retroperitoneal fibrosis, Lancet 2006 Jan 21;367(9506):241-251.)

Retroperitoneal Tumors

A variety of primary and secondary masses may present within the retroperitoneum. The majority of these masses are malignant, the most common of which are sarcomas, composing more than 50% of cases, followed by lymphomas and carcinomas. Primary tumors arising from the retroperitoneal organs include renal cell carcinoma, colorectal and pancreatic adenocarcinoma, adrenal masses, and lymphomas. Lymphatic metastases are also a common retroperitoneal finding, particularly in gonadal cancers, which may present with large para-aortic lymph nodes. Lymphoma is associated
with systemic symptoms including fever, night sweats, and weight loss (>10% of body weight), whereas the majority of other primaries arising within the retroperitoneum are likely to present with minimal systemic symptoms and may only be associated with weight loss or changes in gastrointestinal or urinary function.

RETROPERITONEAL SARCOMA

Retroperitoneal sarcomas account for more than half of all retroperitoneal tumors, with an annual incidence of 0.5 to 1 per 100,000 annually in the United States.\textsuperscript{77} Soft tissue sarcomas are tumors of mesenchymal origin and include over 50 different histologic subtypes.\textsuperscript{78} While the majority of soft tissue sarcomas arise within the extremities, the retroperitoneum is the second most common site of primary disease, and the most common histologic subtypes within the retroperitoneum include liposarcoma (41%), leiomyosarcoma (25%), and malignant fibrous histiocytoma.\textsuperscript{76,77,79,80}

Retroperitoneal sarcomas typically present within the sixth to seventh decade, with no sex or racial predominance.\textsuperscript{79} The majority of patients present with large tumors, with up to 50% of retroperitoneal sarcomas measuring over 20 cm at the time of diagnosis.\textsuperscript{79} Patients often report vague symptoms such as abdominal fullness or distention; acute symptoms such as pain or obstruction are rare.\textsuperscript{76,81,82} On physical exam, a palpable mass is often present.

Recently, several international sarcoma collaborative groups have developed guidelines for the diagnosis and management of retroperitoneal sarcomas, with the overarching recommendation that sarcomas be managed by an experienced multidisciplinary team with specialization in sarcoma (Fig. 18-4).\textsuperscript{77-79,83-85} Preliminary workup includes a CT of the abdomen and pelvis with intravenous contrast, which can help with diagnosis as well as staging. CT can provide information on regional and distant metastases and suggest the histologic subtype. MRI has also been used and, in many cases, may more clearly define tissue planes when determining resectability. Upon identification of a retroperitoneal mass suspicious for sarcoma, an image-guided percutaneous coaxial core needle biopsy is strongly recommended.\textsuperscript{78,83,86} Fine-needle aspirations are typically low yield and therefore not recommended. All tissue biopsies should be reviewed by an
experienced sarcoma pathologist, as 6% to 10% of cases originally designated as sarcoma are in fact not sarcoma and 14% to 27% are assigned the wrong histologic subtype. After confirmation of diagnosis through a tissue biopsy, adequate staging should additionally include a chest CT to rule out pulmonary metastases.

FIGURE 18-4 National Comprehensive Cancer Network guidelines for management of retroperitoneal/intra-abdominal soft tissue sarcoma. CT, computed tomography; CTx, chemotherapy; H&P, history and physical examination; IORT, intraoperative radiation therapy; MRI, magnetic resonance imaging; RT, radiation therapy. (Reproduced with permission from Kneisl JS, Coleman MM, Raut CP: Outcomes in the management of adult soft tissue sarcomas, J Surg Oncol. 2014 Oct;110(5):527-538.)

Staging guidelines for sarcomas (both extremity and retroperitoneal) developed by the American Joint Committee on Cancer (AJCC) depend on grade, tumor size, tumor depth, and presence of lymph node or distant metastases. Unfortunately, the AJCC guidelines are poorly suited for soft tissue sarcomas in general, as the majority are >5 cm, rarely if ever develop nodal metastasis, and have significant heterogeneity due to the variability in site of primary disease and histologic subtype. Several recent studies have
developed sarcoma-specific prognostic models or nomograms that provide a more accurate and patient-specific outcome prediction for patients with soft tissue sarcomas. These nomograms have been further refined to be site and histology specific. The most comprehensive prognostic model or nomogram for retroperitoneal sarcomas was recently published by Gronchi et al and is included in Figure 18-5.

**FIGURE 18-5** Nomogram for 7-year overall survival (OS) in patients with retroperitoneal soft tissue sarcoma. Instructions: The nomogram allows the user to obtain the 7-year OS probability corresponding to a patient’s combination of covariates. For instance, locate the patient’s tumor size and draw a line straight upward to the “Points” axis to determine the score associated with that size. Repeat the process for the additional covariates. Determine the sum of the scores achieved for each covariate and locate this sum on the “Total Points” axis. Draw a line straight down to the “7-year OS” axis to find the predicted probability. DD lipo, dedifferentiated liposarcoma; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD lipo, well-differentiated liposarcoma. (Reproduced with permission from Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-
Surgical resection remains the mainstay of treatment for retroperitoneal sarcomas. The rare cases that are classified as unresectable are typically due to extensive vascular invasion. 86 If a mass is deemed resectable, en bloc complete resection is recommended. 77,78,83 Multiple studies have demonstrated that the best, if not only, opportunity for curative resection is in the setting of primary disease. A thorough discussion of the extent of possible organ resection should be carried out with the patient prior to surgery. The most commonly resected organs include kidney (32%-46%), colon (25%), adrenal (18%), pancreas (10%-15%), and spleen (10%). 76 Due to poor outcomes associated with enucleation and partial resections, these procedures are not recommended and should not be done.

While there is some evidence of improved disease-free and overall survival in extremity sarcomas with multimodal therapy (neoadjuvant or adjuvant chemoradiation therapy), to date, there is no proven benefit of either neoadjuvant or adjuvant external-beam radiation or chemotherapy for the majority of retroperitoneal sarcomas. 76,77,80,82 Retrospective studies have demonstrated a decreased risk of local recurrence and a longer recurrence-free interval with neoadjuvant or adjuvant radiation therapy, but unlike the studies in high-grade extremity sarcomas, this has yet to be proven in a prospective manner. 79 At present, there is an effort by multiple cancer centers nationwide and the National Cancer Institute to evaluate the impact of radiation therapy and chemotherapy in the adjuvant and neoadjuvant setting for retroperitoneal sarcoma; the results are still pending. That being said, most experienced sarcoma centers tend to extrapolate the success of radiation therapy in extremity soft tissue sarcomas to retroperitoneal disease and therefore advocate for preoperative radiotherapy in high-grade lesions to reduce the radiation dose to visceral structures and improve resectability. In addition, certain histologic subtypes that are sensitive to systemic therapy do occur in the retroperitoneum (eg, pancreatic neuroendocrine tumors, gastrointestinal stromal tumors, myxoid round cell liposarcoma) and should be treated with the appropriate systemic agent. Regardless, preoperative and pretreatment planning is best handled in the context of a multidisciplinary sarcoma program.

Prognosis is influenced by many clinicopathologic factors as outlined in...
the nomogram, with the 3 most influential being resection status (R0, R1, or R2), tumor grade, and histologic subtype. Given the overall poor prognosis, there is no role for an incomplete resection of a retroperitoneal sarcoma. Similarly, patients with positive margins have reduced disease-specific survival and a much higher risk of developing metastatic disease. For patients with positive margins, median survival is approximately 18 months, equivalent to that of patients who do not undergo resection. In those with negative margins, there is still a relatively high rate of recurrence, ranging from 40% to 91% in various studies, with median time to recurrence reported as less than 5 years. Overall 5-year survival for patients with complete resection is 54% but is heavily influenced by grade, with reports of 74% for grade 1 and 24% for grade 2 or 3 disease. Given that the risk of recurrence does not appear to plateau in series with long-term follow-up, it is recommended that patients be followed indefinitely. The current National Comprehensive Cancer Network guidelines for surveillance recommend follow-up with physical exam and imaging (CT of chest, abdomen, and pelvis) every 3 to 6 months for a period of 2 to 3 years and then annually.

REFERENCES


53. Sunga KL, Bellolio MF, Gilmore RM, Cabrera D. Spontaneous retroperitoneal hematoma:


74. Caiafa RO, Vinuesa AS, Izquierdo RS, Brufau BP, Ayuso Colella JR, Molina CN. Retroperitoneal
ABDOMINAL TRAUMA

L.D. Britt • Jessica Burgess

OVERVIEW

No anatomical region or cavity is exempt when addressing injuries sustained when managing multi-trauma patients, especially if the traumatic injury is the result of a blunt mechanism. This cornerstone principle is the paramount rationale for the two-tier, systematic approach for the injured patient. In most settings, the acute care surgeon (a specialist who has expertise in trauma, critical care, and emergency general surgical management) is heavily involved in every aspect of care of the trauma patient. Abdominal trauma, regardless of the mechanism of injury, can present many challenging situations, even for the most well trained and talented surgeon. With the pendulum continuing to move more toward nonoperative/selective management of abdominal trauma due to enhanced diagnostic modalities, the hazards of missed or delayed diagnoses are well known and equally well respected. The unevaluable abdomen in a patient who has an associated closed head injury or substantial intoxication with a depressed sensorium remains a perplexing dilemma, irrespective of an unprecedented myriad of advanced technology designed to detect the sequence of intra-abdominal injury.
In addition, there are special populations (the elderly, immunosuppressed, anticoagulated, morbidly obese, etc.) that pose unique management challenges. While the explosion of laparoscopic intervention has made an indelible imprint on practically every surgical discipline, its impact on trauma management has been mostly diagnostic in the hemodynamically normal patients, as opposed to therapeutic management of the injured patient. With the hemodynamically compromised patient being the prototypical individual who is taken to the operating room for exploration, a laparoscopic approach would be an absolute contraindication in that cohort of patients.

Traumatic injury remains the leading cause of death both in the United States and worldwide, resulting in enormous economic and societal losses. In many regions of the world, there is a significant shortage of surgical specialists and general surgeons. This is particularly problematic given the fact that it is the general surgeon specialist who still provides the bulk of emergency surgical care. Given the fact that there are many regions of the country and the world without established trauma systems, this chapter is as applicable to the general surgeon as it is to the trauma surgeon.

Initial Management

Even though the abdomen remains one of the most critical and vulnerable anatomic regions in blunt trauma, a standard, systematic approach of the entire patient must always be conducted—without exception. An initial assessment of the entire patient is imperative before focusing on the specific anatomical region where there is an obvious traumatic injury. The concept of initial assessment includes the following components: (1) rapid primary survey, (2) resuscitation, (3) detailed secondary survey (evaluation), and (4) reevaluation. Such an assessment is the cornerstone of the Advanced Trauma Life Support (ATLS®) program. Integrated into primary and secondary surveys are specific adjuncts. Such adjuncts include the application of electrocardiographic monitoring and the utilization of other monitoring modalities such as arterial blood gas determination, pulse oximetry, the measurement of ventilatory rate and blood pressure, insertion of urinary and/or gastric catheters, and incorporating necessary x-rays and other diagnostic studies when applicable, such as focused abdominal sonography for trauma (FAST) exam, other diagnostic studies (plain radiography of the spine/chest/pelvis and computed tomography [CT]). The initial assessment
essentially underscores the prioritization of patient management. Determination of the status of an airway and optimal oxygenation (airway [A] and breathing [B]) are inevitably the top priorities followed by assessing the adequacy of blood flow—circulation (C). For example, when an airway is believed to be inadequate, the establishment of a rapid-sequence translaryngeal endotracheal intubation might be indicated, or if circulation is deemed suboptimal and bleeding is suspected, an expeditious search for external or cavitary (peritoneum, thorax) source is conducted. Following the “ABCs” of the primary survey is a rapid assessment of the neurological status for gross disability (D)—including determining (1) the level of consciousness, (2) motor function (extremity movement), (3) sensory function, and (4) the presence of reflexes (pupillary, bulbocavernous). This rapid neurologic assessment allows for the calculation of a Glasgow Coma Score (GCS). The last component of the primary survey is ensuring that full exposure (E) of the patient is achieved, along with environmental control, in order to lessen the chance of the patient becoming hypothermic.

The focus of the primary survey is to both identify and expeditiously address immediate life-threatening injuries. In addition to resuscitation, the necessary adjuncts to the primary survey (and secondary evaluation) include electrocardiographic monitoring, placement of urinary and gastric catheters (when appropriate and not contraindicated), along with the close monitoring of physiologic parameters such as respiratory rate, pulse rate, blood pressure, pulse pressure, arterial blood gases, body temperature, and urinary output. Only after the primary survey is completed (including the initiation of resuscitation) and hemodynamic stability is addressed should the secondary survey be conducted, which entails a head-to-toe (and back-to-front) physical examination, along with a more detailed history. Normalization of all vital functions should be evident before proceeding to the secondary survey.

PRIMARY SURVEY

Only the emergency care disciplines of surgery/medicine have a two-tier approach to their initial assessment of the patient, with primary and secondary surveys being integral components. As highlighted above, the primary survey is designed to quickly detect life-threatening injuries. Therefore, a universal approach has been established with the following prioritization:
• Airway maintenance (with protection of the cervical spine)
• Breathing (ventilation)
• Circulation (including hemorrhage control)
• Disability (neurologic status)
• Exposure/environmental control

Such a systematic and methodical approach (known as the ABCDEs of the initial assessment) greatly assists the surgical/medical team in the timely management of those injuries that could result in a poor outcome.

A. **Airway assessment management (along with cervical spine protection):** Because loss of a secure airway could be lethal within 4 minutes, airway assessment/management always has the highest priority during the primary survey of the initial assessment of any injured patient, irrespective of the mechanism of injury or the anatomical wound. The chin lift and jaw thrust maneuvers are occasionally helpful in attempting to secure a patient airway. However, in the trauma setting, the airway management of choice is often translaryngeal, endotracheal intubation. If this cannot be achieved due to an upper airway obstruction or some technical difficulty, a surgical airway (needle or surgical cricothyroidotomy) should be the alternative approach. No other management can take precedence over obtaining an appropriate airway control. Until adequate and sustained oxygenation can be documented, administration of 100% oxygen is required.

B. **Breathing (ventilation assessment):** An airway can be adequately established and optimal ventilation still not be achieved—for example, when there is an associated tension pneumothorax. Other examples include a substantial hemothorax, open pneumothorax, or a large flail chest wall segment. Worsening oxygenation and an adverse outcome would ensue unless such problems are expeditiously addressed. Therefore, assessment of breathing is imperative, even when there is an established and secure airway. A patent airway but poor gas exchange will still result in a poor outcome. Tachypnea, absent breath sounds, percussion hyperresonance, distended neck veins, and/or tracheal deviation are all consistent with inadequate gas exchange. Decompression of the pleural space with a needle/chest tube insertion should be the initial intervention for a pneumo/hemothorax that compromises a patient’s respiratory and/or
cardiovascular status. A large flail chest, with underlying pulmonary contusion, will likely require endotracheal intubation and administration of positive pressure ventilation.

C. **Circulation assessment (adequacy of perfusion management):** The most important initial step in determining adequacy of circulatory perfusion is to quickly identify and control any active source of bleeding, along with restoration of the patient’s blood volume with crystalloid fluid resuscitation and blood products, if required. Decreased levels of consciousness, pale skin color, slow (or nonexistent) capillary refill, cool body temperature, tachycardia, or diminished urinary output are all suggestive of inadequate tissue perfusion. Optimal resuscitation requires the insertion of two large-bore intravenous lines and infusion of crystalloid fluids (warmed). Adult patients who are severely compromised will require a fluid bolus (2 liters of Ringer lactate or saline solution). Children should receive a 20 mL/kg fluid bolus. Blood and blood products are administered as required. Along with the initiation of fluid resuscitation, emphasis needs to remain on identifying the source of active bleeding and stopping the hemorrhage. For a patient in hemorrhagic shock, the source of blood loss will be an open wound with profuse bleeding, or within the thoracic or abdominal cavity, or from an associated pelvic fracture with venous and/or arterial injuries. Disposition (operating room, angiography suite, etc.) of the patient depends on the site of bleeding. For example, a FAST assessment that documents substantial blood loss in the abdominal cavity in a patient who is hemodynamically labile dictates an emergency celiotomy. However, if the quick diagnostic workup of a hemodynamically unstable patient who has sustained blunt trauma demonstrates no blood loss from an open wound in the abdomen or chest, then the source of hemorrhage would likely be from a pelvic injury, necessitating angiography/embolization of a probable arterial injury, if external stabilization (eg, a commercial wrap or binder) of the pelvic fracture fails to stop the bleeding. Profuse bleeding from open wounds can usually be addressed by application of direct pressure or occasionally ligating torn arterial vessels that can easily be identified and isolated.

D. **Disability assessment/management:** Only a baseline neurologic examination is required when performing the primary survey in order to determine neurologic function deterioration that might necessitate surgical intervention. It is inappropriate to attempt a detailed neurologic
examination initially. Such a comprehensive examination should be done during the secondary survey or evaluation. This baseline neurologic assessment could be the determination of the GCS, with an emphasis on the best motor or verbal response, and eye opening. An alternative approach for a rapid neurologic evaluation would be the assessment of the pupillary size and reaction, along with establishing the patient’s level of consciousness (alert, responds to visual stimuli, responds only to painful stimuli, or unresponsive to all stimuli). The caveat that must be highlighted is the fact that neurologic deterioration can occur rapidly, and that a patient with a devastating injury can have a lucid interval (e.g., epidural hematoma). Because the leading causes of secondary brain injury are hypoxia and hypotension, adequate cerebral oxygenation and perfusion are essential in the management of a patient with neurologic injury.

E. **Exposure/environmental control:** In order to perform a thorough examination of a patient, he/she must be completely undressed. This often requires cutting off the garments to safely expedite such exposure. However, care must be taken to maintain normothermia and prevent the patient from becoming hypothermic. Adjusting the room temperature and infusing warmed intravenous fluids can help establish an optimal environment for the patient.

**SECONDARY SURVEY**

As noted earlier, the secondary survey should not be done until the primary survey has been completed and resuscitation initiated, with some evidence of normalization of vital signs. It is imperative that this head-to-toe (front and back) evaluation be performed in a detailed and systematic fashion in order to detect less obvious or occult injuries. This is particularly important in the unevaluable (e.g., head injury or severely intoxicated) patient. The management of blunt abdominal trauma continues to evolve more in the nonoperative arena, as opposed to surgical intervention. The workup has shifted largely from the use of physical exam, plain x-ray, laboratory findings, and diagnostic peritoneal lavage (DPL) to the extensive use of CT and ultrasonography. Treatment for visceral injury has traditionally been surgical, but many forms of solid organ injury can now be successfully managed nonoperatively or with minimally invasive and interventional radiology techniques. Management of the multiple injured trauma patient at
Level I trauma centers, with state-of-the-art techniques, has now conclusively shown significantly improved patient outcomes and survival.\(^2\)

**Diagnostic and Imaging Techniques**

**DIAGNOSTIC PERITONEAL LAVAGE**

DPL has now been essentially supplanted by the adoption and now popularity of abdominal sonography. The utilization of DPL has diminished substantially. Originally described by Root in 1965, DPL was once a mainstay in the management of blunt abdominal trauma for over four decades.\(^3\) Before the era of routine CT scanning, it was used as a screening tool to evaluate patients having blunt or penetrating abdominal trauma with an accuracy rate reported between 92% and 98%.\(^4\)–\(^9\) CT scans and FAST are now the diagnostic modalities of choice in assessment of the injured patient. However, DPL remains an excellent tool for further workup of occult bowel injury or in unstable patients when FAST is not available or has questionable findings. In the workup for occult bowel injury, traditional parameters (Table 19-1) should be used to guide therapy. In unstable patients and when FAST is not an option, a diagnostic tap is usually all that is necessary, and exploration is indicated when there is aspiration of greater than 10 mL of gross blood.

<table>
<thead>
<tr>
<th>Any Viscus</th>
<th>Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mL gross blood</td>
<td>Bacteria</td>
</tr>
<tr>
<td>&gt;100,000 red blood cell/µL</td>
<td>Bile</td>
</tr>
<tr>
<td>&gt;500 white blood cell/µL</td>
<td>Food particles</td>
</tr>
<tr>
<td>&gt;75 IU/liter amylase</td>
<td></td>
</tr>
</tbody>
</table>

The pitfalls of DPL are a relatively high false positive rate, risk of creating visceral injury, and poor sensitivity for detecting injury to retroperitoneal structures such as the pancreas and duodenum.\(^10\)–\(^12\) Iatrogenic events are minimized if a Foley catheter and nasogastric tube are placed prior to the procedure. Patients with pelvic fractures and suspected retroperitoneal
hematoma or pregnant females should undergo a supra-umbilical approach. Visceral injury is less likely with an open approach but more time-consuming and invasive.\textsuperscript{13–16} Checking amylase or lipase in the lavage sample, concomitant use of CT scan, and high index of suspicion are necessary to avoid missed retroperitoneal injury.

FOCUSED ABDOMINAL SONOGRAPHY FOR TRAUMA

In the diagnostic assessment of the acutely injured patient, the bedside ultrasonography for detection of cardiac and intra-abdominal injury is considered the standard of care. Because focused abdominal sonography for trauma is of a noninvasive nature, this diagnostic modality allows the operator to perform an exam simultaneously during the initial resuscitation and stabilization of a multiple injured trauma patient. Due to the relative insensitivity of abdominal examination in the severely injured patient, this technique may provide evidence of significant hemorrhage early in the course of an evaluation. An ultrasound probe is used to examine four key windows for fluid; the subxiphoid area permits visualization of the pericardium, the left subcostal area visualization of the splenorenal recess, right subcostal area visualization of Morison pouch, and the suprapubic area visualization of the pelvic cul de sac (Fig. 19-1). The presence of fluid may indicate presence of cardiac tamponade (fluid in the pericardial space), intra-abdominal hemorrhage, hollow viscus perforation, hemoperitoneum, or ascites. False positive results secondary to preexisting ascites or false negatives due to operator error and/or body habitus are the main limitations. Scanning the suprapubic area with distension of the urinary bladder will enhance the sensitivity of the exam for the detection of pelvic fluid.
FIGURE 19-1  Schematic showing sonographic windows for (1) subxyphoid, (2) left subcostal, (3) right subcostal and (4) suprapubic areas. Distension of the urinary bladder either prior to Foley catheter placement or by installation of 150 to 200 mL normal saline will enhance sensitivity. (Reproduced with permission from Rozycki GS, Ochsner MG, Schmidt JA, et al: A prospective study of surgeon-performed ultrasound as the primary adjuvant modality for injured patient assessment, J Trauma 1995 Sep;39(3):492-498.)
A threshold of at least 200 mL of fluid in the abdominal cavity is necessary for detection, and intra-abdominal injuries must be associated with the presence of this much free fluid for a positive finding.\textsuperscript{17} Reported sensitivities range between 73\% and 88\% and specificity between 98\% and 100\%.\textsuperscript{18} Accuracy rates range from 96\% to 98\%. FAST is an inexpensive, rapid, portable, noninvasive technique that can be performed in serial fashion if there is a change in patient stability.\textsuperscript{19–21} In addition, it obviates the risk of exposing pregnant females to radiation. Positive findings in stable patients can be further evaluated with CT, while unstable patients with a positive finding should prompt the surgeon to take the patient to the operating room for emergent exploration. Workup of a patient with a reliable abdominal exam may be complete with a negative FAST in the absence of abdominal signs or symptoms.

**COMPUTED TOMOGRAPHY**

Steady advances in the technology and speed of CT have continued to be an integral part of the diagnostic management of trauma patients. Multidetector scanners have drastically improved resolution and accuracy of these imaging studies. Negative predictive values as high as 99.63\% have been reported for patients sustaining significant mechanisms of blunt trauma allowing the use of CT as a reliable and noninvasive screening tool for screening patients with blunt abdominal trauma.\textsuperscript{22} In light of modern-day CT capabilities, prospective data have demonstrated that patients with a significant mechanism and a benign abdomen can be released from the emergency department if a CT scan of the abdomen shows no evidence of visceral injury provided that there are no other reasons for hospitalization.\textsuperscript{22}

CT reliably identifies injuries in solid organs such as the spleen, liver, and kidney because of the associated vascular nature demonstrating disruption of normal architecture, associated free fluid, and the so-called vascular blush.\textsuperscript{23} Established grading scales continue to be used for accurate classification and determination of management plan (Tables 19-2 through 19-4).\textsuperscript{23,24}
<table>
<thead>
<tr>
<th>Grade*</th>
<th>Injury Description</th>
<th>ICD-10b</th>
<th>AIS-90c</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma, Subcapsular, &lt;10% surface area</td>
<td>S36.02A</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laceration, Capsular tear, &lt;1 cm parenchymal depth</td>
<td>S36.03A</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma, Subcapsular, 10-50% surface area; intraparenchymal, &lt;5 cm in diameter</td>
<td>S36.02A</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laceration, 1-3 cm parenchymal depth which does not involve a trabecular vessel</td>
<td>S36.03A</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma, Subcapsular, &gt;50% surface area or expanding; ruptured subcapsular or</td>
<td>S36.02A</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>parenchymal hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laceration, Intraparenchymal hematoma &gt;5 cm or expanding &gt;3 cm parenchymal depth or</td>
<td>S36.03A</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>involving trabecular vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Laceration, Laceration involving segmental or hilar vessels producing major</td>
<td>S36.032</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>devascularization (&gt;25% of spleen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Laceration, Completely shattered spleen</td>
<td>S36.032</td>
<td>5</td>
</tr>
<tr>
<td>Vascular</td>
<td>Hilar vascular injury which devascularizes spleen</td>
<td>S36.032</td>
<td>5</td>
</tr>
</tbody>
</table>

*Advance one grade for multiple injuries, up to grade III.

1ICD, International Classification of Diseases, 10th Revision.

AIS, abbreviated Injury score.


### TABLE 19-3: LIVER INJURY GRADING SYSTEM

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Injury Description</th>
<th>ICD-10b</th>
<th>AIS-90c</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma, Subcapsular, &lt;10% surface area</td>
<td>S36.112</td>
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<tr>
<td></td>
<td>Laceration, Capsular tear, &lt;1 cm parenchymal depth</td>
<td>S36.114</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma, Subcapsular, 10%-50% surface area; intraparenchymal, &lt;10 cm diameter</td>
<td>S36.112</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laceration, 1-3 cm parenchymal depth, &lt;10 cm in length</td>
<td>S36.115</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma, Subcapsular, &gt;50% surface area or expanding; ruptured subcapsular or</td>
<td>S36.116</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>parenchymal hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laceration, Intraparenchymal hematoma &gt;10 cm or expanding &gt;3 cm parenchymal depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laceration, Parenchymal disruption involving 25%-75% of hepatic lobe or 1-3 Couinaud</td>
<td>S36.116</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>segments within a single lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Laceration, Parenchymal disruption involving &gt;75% of hepatic lobe or &gt;3 Couinaud</td>
<td>S36.116</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>segments within a single lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Vascular, Juxtahepatic venous injuries; ie, retrohepatic vena cava/central major</td>
<td>S36.116</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>hepatic veins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Vascular, Hepatic avulsion</td>
<td>S36.116</td>
<td>6</td>
</tr>
</tbody>
</table>

*Advance one grade for multiple injuries, up to grade III.

1ICD, International Classification of Diseases, 10th Revision.

AIS, abbreviated Injury score.


### TABLE 19-4: ORGAN INJURY SCALE FOR THE KIDNEY OF THE AMERICAN ASSOCIATION OF THE SURGERY OF TRAUMA

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Injury Description</th>
<th>ICD-10b</th>
<th>AIS-90c</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma, Subcapsular, &lt;10% surface area</td>
<td>S36.02A</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laceration, Capsular tear, &lt;1 cm parenchymal depth</td>
<td>S36.03A</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma, Subcapsular, 10-50% surface area; intraparenchymal, &lt;5 cm in diameter</td>
<td>S36.02A</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laceration, 1-3 cm parenchymal depth which does not involve a trabecular vessel</td>
<td>S36.03A</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma, Subcapsular, &gt;50% surface area or expanding; ruptured subcapsular or</td>
<td>S36.021</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>parenchymal hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laceration, Intraparenchymal hematoma &gt;5 cm or expanding &gt;3 cm parenchymal depth or</td>
<td>S36.031</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>involving trabecular vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Laceration, Laceration involving segmental or hilar vessels producing major</td>
<td>S36.032</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>devascularization (&gt;25% of spleen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Laceration, Completely shattered spleen</td>
<td>S36.032</td>
<td>5</td>
</tr>
<tr>
<td>Vascular</td>
<td>Hilar vascular injury which devascularizes spleen</td>
<td>S36.032</td>
<td>5</td>
</tr>
</tbody>
</table>

*Advance one grade for multiple injuries, up to grade III.

1ICD, International Classification of Diseases, 10th Revision.

AIS, abbreviated Injury score.

Detection of bowel injury via CT scan in patients who are intoxicated, intubated, or who have associated closed head injury or other distracting injuries, can present a diagnostic challenge in the absence of a reliable abdominal exam. The incidence of blunt bowel injury varies from series to series but is generally reported in the 1% to 5% range in all blunt trauma patients admitted to Level I trauma centers.25,26 A high index of suspicion is predicated on mechanism of injury and physical exam findings, such as abdominal wall ecchymosis, tattooing, and/or seatbelt sign. CT findings may be overt such as extravasation of oral contrast or pneumoperitoneum, or more commonly subtle findings such as bowel wall thickening, stranding of the mesentery, or free fluid in the absence of solid organ injury. Indirect findings may be fairly nonspecific and secondary to bowel edema from resuscitation or preexisting ascites. Reproductive age females may have a small amount of normal or “physiologic” pelvic fluid present, sometimes adding to the complexity of the evaluation. Patients on positive pressure ventilation or with significant barotrauma may develop mediastinal or subcutaneous emphysema that can track through the peritoneum or retroperitoneum and give the appearance of free air. Great care in the radiologic interpretation and close clinical correlation are necessary in such cases. The liberal use of diagnostic modalities (eg, abdominal CT scan) in the hemodynamically normal injured patient may prevent nontherapeutic laparotomies. Obviously, when significant doubt remains, abdominal exploration may be required to confirm an injury.

The role of oral contrast in evaluation of the acutely injured patient has recently come under question. Little time is usually available in the
emergency setting to permit adequate opacification of the small bowel. Patients are further at risk for aspiration of the contrast media, and administration often requires placement of a nasogastric tube. There have been several reports that have shown that elimination of oral contrast media does not lead to an increased incidence of missed bowel injury.\textsuperscript{25–27} Many centers have now safely eliminated the use of oral contrast media from their routine trauma protocols, expediting management and ease of patient care. Resuscitation edema may cause a hazy appearance around the head of the pancreas and duodenal c-loop, raising the question of a pancreas or duodenal injury. Further clarification in this situation can be obtained when it occasionally occurs via repeat CT scan with the administration of oral contrast and the injection of a 300- to 500-cc bolus of air down the nasogastric tube in order to make pneumoperitoneum obvious.

CT may also be of great importance in identifying patients with arterial hemorrhage related to pelvic fracture. CT imaging may demonstrate an arterial blush or large hematoma in the vicinity of a pelvic fracture indicating the need for pelvic arteriography or pelvic external fixation. A “CT cystogram” may also be helpful and eliminate redundancy of radiographic evaluation. The Foley catheter is clamped after placement in the trauma bay. Real-time interpretation of the CT scan is performed by the evaluating physician, which may dictate further delayed images or a formal three-view (anterior/posterior, lateral, and postvoid views) cystogram.

**SPECIFIC CONSIDERATION FOR BLUNT TRAUMA**

**The Bowel**

There is yet no place for nonoperative management of hollow viscus injury, and the nemesis of nonoperative management of blunt abdominal trauma is therefore the missed bowel injury and all its catastrophic consequences. Otherwise, most management is straightforward: debridement and primary repair for nondestructive injuries and resection with primary repair versus stomal formation for destructive injuries.
RADIOGRAPHIC FINDINGS OF BLUNT BOWEL INJURY

There are two basic types of findings of bowel injury on CT scan: direct and indirect. Direct findings are usually straightforward if present and amount to extravasation of oral contrast (if administered) and free air, which have been reported to occur in 4% and 28% of the time, respectively. Little else can explain the first of these two entities, while free air from other sources such as extensive subcutaneous emphysema tracking through a diaphragmatic hiatus is unusual.\textsuperscript{28–30} Such findings may be subtle and can vary in presentation depending on the quality of the scan. Indirect findings include mesenteric hematoma or contrast blush, bowel wall edema, unexplained free fluid, “fat streaking,” and bowel loops that do not opacify with intravenous contrast (\textit{Table 19-5}).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Direct} & \textbf{Indirect} \\
\hline
Oral contrast extravasation & Mesenteric hematoma  \\
Free air & Mesenteric blush  \\
 & Bowel wall edema  \\
 & Unexplained ascites  \\
 & Fat streaking  \\
 & Unopacified (vascular contrast media) bowel loops  \\
\hline
\end{tabular}
\caption{CT Scan Findings of Blunt Bowel Injury}
\end{table}

Mesenteric hematoma is nonspecific and can occur from associated injuries, such as pelvic fractures or renal injuries, with hematomas from these structures expanding into the bowel mesentery. However, a vascular blush in the leaves of the mesentery is indicative of active hemorrhage until proven otherwise, and generally is a determinant for immediate operative exploration. Bowel wall edema and ascites are common in blunt trauma patients, can occur from resuscitation of other injuries, and do not necessarily connote bowel injury. Free fluid in the absence of solid organ injury can be further evaluated with DPL if the abdominal exam is unreliable. Fat streaking can occur with mesenteric contusion and does not necessarily portend an operative indication. Unopacified bowel loops can indicate vascular
disruption of the mesentery or simply be due to poor contrast timing in an under-resuscitated patient. Evidence of these findings increases the likelihood of finding an injury at exploration when there is an increasing number of these findings.

OPERATIVE MANAGEMENT

Appreciation of the American Association for the Surgery of Trauma (AAST) organ injury grading scale is helpful in describing wounds of the bowel. Grade I injuries are contusions and partial thickness lacerations of the bowel wall without perforation. Grade II injuries are full thickness wounds involving less than 50% of the bowel wall circumference. Grade III are lacerations comprising greater than 50% of the bowel wall circumference without complete transection. Grades IV and V injuries represent complete transection of the bowel wall and transection with segmental tissue loss and/or devascularization of the mesentery, respectively. The terms destructive and nondestructive simplify the terminology; nondestructive wounds are those injuries that can be managed with debridement and primary-suture enterorrhaphy and are comprised of grades I through III. Destructive wounds require resection of an entire segment of the bowel due to loss of colonic integrity or devascularization of the mesentery and encompass grades IV and V (Tables 19-6 and 19-7).

### TABLE 19-6: AAST SMALL BOWEL INJURY SCALE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Type of Injury</th>
<th>Description of Injury</th>
<th>ICD-10&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AIS-90&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma</td>
<td>Contusion or hematoma without devascularization</td>
<td>S36.429A</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>Partial thickness, no perforation</td>
<td>S36.439A</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>Laceration</td>
<td>Laceration &lt;50% of circumference</td>
<td>S36.439A</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>Laceration</td>
<td>Laceration ≥50% of circumference without transection</td>
<td>S36.439A</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Transection of the small bowel</td>
<td>S36.439A</td>
<td>4</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Transection of the small bowel with segmental tissue loss</td>
<td>S36.439A</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Devascularized segment</td>
<td>S36.499A</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Advance one grade for multiple injuries, up to grade III.

<sup>b</sup>ICD, International Classification of Disease, 10th Revision.

<sup>c</sup>AIS, abbreviated Injury score.

### TABLE 19-7: AAST COLON INJURY SCALE
The distinction between destructive and nondestructive wounds is important in terms of the prescribed management. Nondestructive wounds of the large or small bowel can generally be repaired without further consideration. Most small bowel destructive injuries should be resected and reconstituted unless damage control conditions prevail. In contrast to the small bowel, the management of colon injuries has received great scrutiny. Ushering in the dawn of modern-day trauma surgery, the World War II military experience dictated that all colon wounds, destructive or not, be managed by colostomy. This philosophy remained surgical dogma until the 1980s. In a comprehensive review of the literature since 1979, primary repair of the colon for nondestructive wounds was shown to have a leak rate of 1.6%. Compared to patients receiving colostomy for similar types of wounds, the incidence of intra-abdominal abscess was 4.9% for primary repair and 12% for colostomy, and overall complication rate was 14% for primary repair and 30% for colostomy. Mortality rates were similar at 0.11% for primary repair and 0.14% for colostomy. These findings clearly show the superiority of primary repair for nondestructive wounds of the colon.

Several risk factors for anastomotic failure pertaining to destructive colon injury have been addressed in the literature: hypotension, shock, interval from injury to operation, amount of fecal contamination, associated organ injury, transfusion requirement, and comorbid disease. No data have conclusively shown that any of these risk factors increase the likelihood of anastomotic failure. Patients with massive blood loss or shock may be better served by undergoing a damage control procedure, with delay of definitive repair. Interval from injury to repair greater than 12 hours can be a relative contraindication to definitive repair if there is widespread (greater than one quadrant) fecal contamination. Greater than one or two organ system injury has been a concern, but this may just be a marker for degree of shock and overall physiologic derangement. Comorbidities, such as AIDS and cirrhosis,
deserve special consideration and these patients may be better off with the establishment of an ostomy diversion.\textsuperscript{37,38} Patients with any of these risk factors have a higher incidence of intra-abdominal abscess and overall complication rates.\textsuperscript{32}

Notwithstanding the caveats of these comorbidities, colonic resection and primary anastomosis for destructive wounds would be permissible in most trauma settings. In a collective review of 207 patients reported in the literature, management of destructive bowel injury with resection and primary anastomosis had a reported leak rate of 7.2\%, with a mortality of 1.7\% attributable to the colon wound.\textsuperscript{32} In the largest single-institution experience, Murray showed a leak rate of 11\% in 112 patients undergoing resection and primary anastomosis for destructive colon wounds, with two deaths related to leaks.\textsuperscript{39}

In a multi-institutional trial, Demetriades reported 297 patients with destructive colon wounds in which 197 underwent resection and anastomosis and 100 underwent diversion.\textsuperscript{37} The choice of operation was left to the discretion of the attending surgeon at the time of exploration. Not surprisingly, the patients with diversion were significantly more injured and critically ill than those undergoing reestablishment of intestinal continuity. The anastomotic leak rate was 6.6\%, with one leak from the stump of a Hartmann pouch in the diverted group and four deaths related to anastomotic failure. Multivariate analysis showed no significant difference in mortality or abdominal complications between diversion and primary anastomosis groups. The authors concluded that “patients can be managed by primary repair regardless of risk factors.” This study certainly demonstrates a liberal use of resection and primary anastomosis in relatively sick and injured cohort of patients. However, the ultimate decision for the choice of operation was up to the discretion of the surgeon at the time of operation on a case-by-case basis—for which there is no substitute.

At laparotomy, the bowel should be examined in its entirety after all other sources of major bleeding are controlled. Small injuries should be noted and tagged with an identifiable suture for easy reference. Larger wounds contributing to ongoing soiling can be temporarily controlled with a whipstitch (quick running suture) or Babcock clamps. Mesenteric injuries are identified and active bleeding controlled appropriately. Attention should be directed to the location of the superior mesenteric artery for injuries
encroaching on the root of the mesentery. Mesenteric hematomas should be explored with ligation of injured vessels and mesenteric defects closed by careful reapproximation of the peritoneal edges so as not to compromise any associated vasculature. Bowel viability should be noted in relation to any mesenteric injury. Clusters of grade I through III injuries may be resected or individually repaired depending on the particular injury pattern. In blunt trauma, there are usually only one or two grade II or III wounds that can be repaired primarily or one or more devitalized segments that require resection.

Small, superficial grade I injuries can be left alone, while deeper, longer grade I injuries can be closed with a simple running suture or interrupted Lembert sutures. Grade II and III wounds should be debrided back to healthy, viable bowel and closed transversely, preventing narrowing of the lumen of the bowel. Single-layer running or interrupted closure is generally sufficient for repair of small bowel. When there is significant bowel wall edema, peritonitis, or soiling, a two-layer closure with a running inner layer and interrupted Lembert outer layer may be preferential. Grade I and II colon wounds may be managed with single-layer closure. However, grade III colon wounds should be closed in two layers for added protection.

The leak rate associated with stapled versus hand-sewn anastomosis for destructive wounds of the bowel has been an area of ongoing controversy. In a two retrospective studies totaling 284 patients undergoing stapled versus hand-sewn anastomosis, Brundage showed that hand-sewn procedures had lower leak rates.\textsuperscript{40,41} Two other retrospective studies totaling 484 patients showed no difference in the leak rate of stapled versus hand-sewn procedures.\textsuperscript{42,43} Brundage’s two studies included 78 colon wounds, while the other studies were confined only to the small bowel. Stapled procedures may be a little quicker, particularly if there is more than one anastomosis. In general, the technique chosen according to the literature can be a matter of surgeon’s preference. However, with edematous bowel, the hand-sewn technique is a more prudent approach.

The Spleen

The spleen is the most commonly injured intra-abdominal organ, followed by the liver and small bowel in blunt trauma patients. The spleen’s location in the left upper quadrant lends susceptibility to injury from broken ribs,
deceleration, and blunt percussion forces. Clinically, patients with splenic injury may present with hypotension, left upper quadrant pain or tenderness to palpation, or diffuse peritonitis from extravasated blood. Referred pain to the left shoulder on deep inspiration in the face of splenic hematoma is known as Kehr sign.

NONOPERATIVE MANAGEMENT

Most series indicate that approximately 60% to 80% of patients presenting with blunt splenic injury can be managed nonoperatively at Level I or II trauma centers.\textsuperscript{44–48} Facilities without the resources and experienced of a bona fide trauma team may not safely meet the demands of nonoperative management and should consider patient transfer.\textsuperscript{49} Patients selected for nonoperative management must have normal vital signs, be free of peritoneal signs or other concern for hollow viscus injury, and have no evidence of free extravasation of intravenous contrast from the splenic parenchyma (Fig. 19-2).
Considerable debate remains regarding risk factors for failure of nonoperative management. Higher AAST splenic injury grade, age greater than 55 years, moderate to large hemoperitoneum, subcapsular hematoma, and portal hypertension have all been suggested to increase the risk of failure. Early reports in the evolution of nonoperative management regarding AAST
grade did not demonstrate higher failure rates for higher-grade injury. More recent reports using high-resolution multidetector CT scanners allow better assessment of injury grade. The data from these studies show patients with injury grades III to V to be at increased risk for nonoperative failure. Age continues to be controversial subject in the literature, with numerous reports claiming that age greater than 55 years either is or is not a risk factor for failure. Documentation of a moderate or large hemoperitoneum is suggestive of a major injury and should be considered a significant factor in individual patient assessment.

Patients with splenic subcapsular hematoma or history of portal hypertension are specific subgroups of patients that deserve special consideration. This cohort of patients with subcapsular hematoma in our experience tend to ooze from the raw parenchymal surface and further disrupt the capsule, leading to more raw surface area to bleed. These patients are at increased risk for delayed rupture 6 to 8 days following injury and may already be discharged from the hospital if they have isolated injury. Furthermore, splenic embolization is not a very effective treatment for this condition because it usually necessitates coiling of the main splenic artery, which can lead to significant pain and abscess formation. History of portal hypertension or cirrhosis, while not an absolute contraindication to nonoperative management, certainly should serve as a caveat. The general risks of laparotomy in a Child–Pugh B or C cirrhotic patient need to be carefully weighed against the risk of ensuing and worsening coagulopathy. This scenario may indeed dictate the need for splenic artery embolization. None of these risk factors alone should dictate the decision to proceed immediately to operative intervention. Nonoperative management does reduce hospital length of stay and transfusion requirement; however, the morbidity of splenectomy should remain low in any surgeon’s hands. Overall, the patient’s condition, including comorbidities, coagulopathy, and other problems (such as traumatic brain injury, aortic injury, and suspicion for concomitant hollow viscus injury) factor into the decision-making process. No one should ever succumb to splenic hemorrhage that was undergoing nonoperative management.

Approximately 20% of patients initially undergoing nonoperative management of blunt splenic injury require further intervention. Failure has been associated with the presence of a contrast blush in up to two-thirds of these patients. The presence of a contained contrast blush within the
parenchyma of the spleen represents pseudoaneurysm formation of a branch of the splenic artery. Angioembolization is now commonly used to selectively occlude the arterial branches containing these injuries.\textsuperscript{44,45,48,52,53} Implementation of this salvage technique at centers that routinely screen for the presence of pseudoaneurysm has increased the success of nonoperative management to 90% or greater. Pseudoaneurysm formation has been observed in even grade I and II injuries, and may not be present on the initial imaging.\textsuperscript{44,47,53} Therefore, follow-up CT scan is recommended on all patients with splenic trauma within 24 to 48 hours after injury. If these images show stable injuries without pseudoaneurysm formation, expectant management can continue.

Long-term data are unavailable concerning the risk of outpatient or delayed rupture, but the incidence is low and has been reported to be about 1.4%.\textsuperscript{54} The average date to readmission for delayed splenectomy after discharge was 8 days in this study. Lower grade (I, II) injuries tend to heal more quickly, and most injuries are healed by 5 to 6 weeks.\textsuperscript{55} However, approximately 20% of blunt splenic injuries will not show complete healing and may be at risk for pseudocyst formation. A CT scan should be repeated in 6 weeks for grade I and II injuries and 10 to 12 weeks in grades III to V before allowing the patient to return to normal activity.

**SPLENECTOMY**

Patients requiring urgent or emergent intervention for splenic hemorrhage may develop hypothermia, coagulopathy, and visceral edema. The most expeditious and safest course of action under these conditions is removal of the spleen. The general assumption of abdominal exploration for trauma is that there are known, and possibly unknown, injuries. The operative approach is via a midline vertical incision that allows the best exposure and facilitates temporary abdominal closure should visceral edema or damage control measures be necessary.

With respect to performing a splenectomy, a self-retaining retractor can be used to expose the left upper quadrant. The spleen is retracted medially, with some downward compression, while taking down the posterior attachments with the cautery. Once these attachments are freed, the spleen can be mobilized medially for optimal exposure. The assistant stands on the left side of the table and supports the spleen while the surgeon ligates short gastric and
hilar vessels. Being careful to avoid the tail of the pancreas, a large clip, placed on the specimen side of the splenic hilum, will reduce back-bleeding and expedite the procedure. Once the spleen has been removed, the splenic fossa is meticulously inspected for further bleeding with a rolled laparotomy pad.

**SPLENORRHAPHY**

Hemodynamically stable patients found to have small to moderate amounts of parenchymal hemorrhage at laparotomy may be candidates for splenic preservation. The spleen is mobilized into the wound using the same technique as for splenectomy. The injury to the spleen is assessed and decision is made whether to resect a portion if the parenchymal injury extends into the hilum or if arterial bleeding is coming from within the splenic laceration itself. If the decision is made to resect the upper or lower pole, the parenchyma is divided with the cautery and the associated hilar vessels are taken with clamps and ties. Any arterial bleeding from the parenchyma is controlled with suture ligature, and the cautery is used to control oozing from the parenchyma. A tongue of omentum is then sutured into the laceration or to the raw surface of the remaining spleen in the case of a partial splenic resection. Approximately 50% of the spleen is required to preserve adequate phagocytic and immunologic function. If this cannot be achieved, a splenectomy is probably the best option.

**OVERWHELMING POST SPLENECTOMY INFECTION**

The incidence of overwhelming post-splenectomy infection (OPSI) following trauma is not well understood because it may not be appreciated when it occurs, along with the fact that it is not routinely reported. However, the reported incidence of OPSI in adult patients undergoing splenectomy for all causes is 0.9%, with a mortality of 0.8%. The risk of OPSI in adults following trauma is felt to be lower than the incidence seen after splenectomy for hematological disorders such as idiopathic thrombocytopenic purpura (ITP), lymphoma, and thalassemia. Children are at greater risk for OPSI and should receive prophylactic penicillin V 125 mg twice daily until age 3 and then 250 mg twice daily until age 5. Currently, anyone greater than 2 years of age should receive the 23 valent pneumococcal vaccine and a one-time dose
of the *Haemophilus influenza* and meningococcal vaccine. A one-time booster dose of the pneumococcal vaccine is recommended 5 years after the original vaccine. 

**Hepatobiliary System**

Blunt trauma contributes over 75% of mechanisms of injuries for most of the trauma centers in the United States. The liver, the largest solid organ in the body, is one of the most frequently injured abdominal organs by either blunt or penetrating mechanisms. Fortunately, the majority of hepatic injuries are not severe and require no surgical repair. These are low-grade injuries (Table 19-8). Suspicion of liver injury is predicated on several factors: clinical suspicion derived from the mechanics of the crash and the hemodynamic state of the patient in the field and upon arrival at the hospital along with findings obtained during abdominal examination obtained in the hospital (Fig. 19-3). High-energy crashes involving application of force to the upper abdomen or to the right thoracoabdominal area should arouse immediate suspicion of a possible hepatic injury. Hemodynamic lability, although not an exclusive feature of liver injury, mandates evaluation to exclude it as the source of the hemorrhage. Tenderness in the right upper quadrant in the absence of other signs can be suggestive of subcapsular hematoma requiring attention and further evaluation. Unfortunately, the physical examination is not perfect and has a false positive rate of approximately 50% and a false negative rate of 40%.

**TABLE 19-8: THE AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA (AAST) LIVER INJURY SCALE (1994 REVISION)**
FIGURE 19-3  Juxtahepatic (or retrohepatic) vena cava is in direct contact with the posterior aspect of the liver.

Additional methods available to evaluate the abdomen include FAST, CT, and DPL. FAST has become a highly reliable test used when seeking to determine whether there is blood in the abdomen in a patient who is hemodynamically labile. In the stable patient in whom liver injury is suspected, the use of CT has become widespread. Several classification schemes have been described for liver injuries. There are inconsistencies in the terminology, but a grading scheme proposed by the AAST is now in wide
These diagnostic adjuncts are not intended to replace clinical judgment and examination by the surgeon. Whatever method is used for abdominal evaluation should be readily available, and the surgeon should be proficient in its use and interpretation.

**APPROACH TO THE INJURED LIVER**

With hepatic injuries, the paramount decision is to determine if an intervention is needed to control hemorrhage. Hemodynamic instability mandates expeditious operative management or angiography/embolization (if the patient can be stabilized with volume resuscitation) in order to make transportation to the radiographic suite less risky for the patient. The hemodynamically stable patient may be evaluated by any of the methods noted earlier. Minor grade I or II injuries frequently require no operative intervention. When diagnosing by CT scan, the surgeon must be cognizant of the magnitude and anatomy of the liver injury. Contusion contained within the liver capsule or minor laceration, such as in grade I or II injuries, may be observed. These diagnoses together constitute most liver injury cases, accounting for 60% or 70%. Grade III injuries (deeper, larger wounds with more tissue destruction) occur in approximately 25% of cases. Grade IV and V injuries, involving large amounts of tissue destruction, have an incidence of 7% and 3%, respectively, and are highly lethal. It should be emphasized that evidence of blood in the peritoneal paracolic gutters, in the pelvis, or tracking along the periportal triads is suggestive of a more significant injury than the liver anatomy may indicate and mandates exploration. In addition, the concomitant existence of hollow viscous injury occurs in 5% and 20% of major hepatic injuries.

It is important to be aware that massive parenchymal injuries can occur with surprisingly little bleeding and that minor lacerations may bleed profusely. An understanding of the tissue architecture of the liver is a prerequisite to successful management. Most blunt lacerations occur along segmental fissures, because the vascular and biliary duct structures are moderately shear resistant. This explains why a large stellate or “bear claw” laceration may be seen with little or no intraperitoneal blood in a hemodynamically stable patient. This can be managed nonoperatively with observation and repeated CT scan. Nonoperative treatment of the stable

use (Table 19-8).
patient sustaining a blunt liver injury is the management approach of choice today. Table 19-9 highlights the reported failure rates for nonoperative management of hepatic trauma.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of Patients</th>
<th>Immediate Surgery (%)</th>
<th>Overall Failure Rate (%)</th>
<th>Liver Failure Rate (%)</th>
<th>Other Failure Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meredith (94)</td>
<td>116</td>
<td>48</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Croce (95)</td>
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<td>18</td>
<td>11</td>
<td>5</td>
<td>6</td>
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<tr>
<td>Pachter (96)</td>
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<td>53</td>
<td>1.2</td>
<td>0.7</td>
<td>0.5</td>
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<tr>
<td>Malhotra (00)</td>
<td>661</td>
<td>15</td>
<td>7</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Velmahos (03)</td>
<td>78</td>
<td>29(^1)</td>
<td>15</td>
<td>0</td>
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</tr>
<tr>
<td>Christmas (05)</td>
<td>561</td>
<td>32(^2)</td>
<td>1.8</td>
<td>0.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

\(^1\)15\% for liver bleeding
\(^2\)13\% for liver bleeding

Conversely, the deceleration forces are responsible for a shear effect that can result in avulsion of the hepatic veins from the vena cava or major branches of the portal venous or hepatic venous systems. Hemorrhage is devastating, difficult to control, and responsible for the high mortality rate seen with such injuries.

Penetrating injuries present their own set of difficulties; missile tracts may bleed profusely. The same elasticity that can protect the vascular structures from shear forces has little if any effect when confronted with a missile.

**INTRAOPERATIVE DECISIONS: GENERAL PRINCIPLES**

Once the decision to operate has been made, the surgeon needs to proceed in an orderly fashion, to a fully equipped operative theater that includes the capabilities of invasive monitoring. Before opening the abdomen, the surgeons must ensure that there is optimal venous access. Large-bore central access is essential. The prudent, historic dictum is that access should be from the upper torso in the event there is a retrohepatic venacaval injury. The blood bank must be notified of the potential for massive transfusion of packed cells and blood components to treat the often associated coagulopathy. The development of blood salvage systems has greatly improved the care of these patients; shed blood from the operative field can
be washed and reinfused, provided there is no evidence of gastrointestinal contamination. Infusion systems are available that allow rapid delivery of large volumes of warmed fluid to help minimize hypothermia and hypovolemia. Hypothermia is a common cause of coagulopathy and must be aggressively defended against. Invasive monitoring capabilities are essential in the management of these critically injured patients.

Optimal surgical exposure is essential and starts with performing a midline vertical incision for expedient entry into the abdominal cavity. The incision should extend from the xiphoid process to the symphysis pubis. Such an approach allows, if necessary, relatively easy extension into the thorax through either a median sternotomy or a lateral thoracotomy.

Performing a celiotomy could potentially decompress the tamponade, thereby necessitating expeditious vascular control. The need to perform an emergency thoracotomy for vascular control of the aorta before opening the abdomen is rarely indicated. Such control of the bleeding can usually be obtained with the assistant’s manual compression of the liver.

Once the abdomen is open, a rapid assessment of the injury is made and priority management begun. All clot is evacuated, and the four quadrants are packed to control bleeding. A sequential examination is then carried out with priority given to control of blood loss followed by control of any enteric content spillage.

The general approach to the liver injury requires adequate visualization of the anatomic features of the injury. This may require mobilization of the liver along the falciform and triangular ligaments. Full mobilization of the liver allows delivery onto the abdominal wall that can often facilitate suture repair of a hepatic wound in a difficult area. When mobilizing the liver, care must be taken that the hepatic veins are not injured. The coronary ligaments are in close proximity to hepatic veins. Also, the surgeon must be cautious during the mobilization of the liver that venous return through the vena cava is not obstructed for a prolonged period. Hemorrhage control during mobilization can often be done by the assistant’s applying direct pressure with laparotomy packs, compressing the liver between the hands.

As noted earlier, most of the injuries encountered are grade I or II and require little more than simple suture repair. Grades III, IV, and V injuries require an organized approach for successful control of hemorrhage, which includes manual compression, direct ligation, or clipping of lacerated vessels along with sophisticated techniques for more complex wounds.
Vascular occlusion of the portal triad (performing the Pringle maneuver) is a useful method of controlling hepatic arterial and portal venous inflow to the liver. A noncrushing or vascular clamp can be applied to the porta hepatis and safely left in place for approximately 45 minutes, although the specific duration threshold is not known for the hemodynamically labile patient. An umbilical tape placed around the porta hepatis structures can also be used for such control. If this maneuver markedly reduces the liver’s bleeding, the parenchymal injury can be assessed and a method of repair decided upon. However, if hemorrhage persists, then an intrahepatic portal vein injury or a major hepatic vein injury must be suspected.

Proceeding with hepatotomy for localization and control of hemorrhage requires fastidious cooperation between the surgeon and the first assistant. With the depth of the hepatic wound exposed, it is usually the first assistant who controls the bleeding. The finger-fracture technique for hepatotomy, with the first assistant compressing the liver, is very effective. The operating surgeon using his/her fingertips or the handle of a scalpel to separate the liver parenchyma and the assistant using a multiple loaded clip applier, made popular for laparoscopic cholecystectomy, ligate severed vessels. Nonabsorbable suture ligation can also be performed to control vessels as each is encountered. Knowledge of the anatomy of the liver (along with reported anatomic variants) is a prerequisite to this approach. The confluence of the left and middle hepatic veins must be kept in mind to avoid overzealous ligation (Fig. 19-4). Likewise, the position of the inferior vena cava and the hepatic veins to the caudate lobe should be noted to avoid unnecessary injury that may complicate surgical management. The placement of random deep sutures is fraught with difficulty. Failure of the abovementioned maneuvers to control hepatic bleeding means that the surgeon either has not adequately identified the source or is dealing with coagulopathic bleeding (or both).
FIGURE 19-4 After obtaining the necessary exposure (thoracotomy, mediasternotomy), an opening—aalong with 2.0 Prolene purse-string suture—is created in the right atrial appendage (A) to provide the access needed for insertion of the atriocaval shunt (B), which is usually a No. 36 chest tube. An extra hole needs to be made at the level of the right atrium. With the chest tube holes being outside of umbilical tape occlusion, blood is directed from
the lower half of the body and the kidney through the atiocaval shunt.

Although ligation of the hepatic artery or portal vein branch supplying a specific portion of the liver is rarely needed, the suspected branch should be isolated, and its occlusion should control hemorrhage while the Pringle maneuver is released. If such is the case, then the identified branch should be ligated.

Liver injury rarely follows the anatomic lines of demarcation delineating the right and left lobes, or the segments. Anatomic resection, a once popular approach, has poor outcome with high mortality rates. This technique has essentially been abandoned. Resectional debridement of devitalized liver is not formal lobectomy but rather a completion of the injury to remove nonviable hepatic tissue and facilitate vascular control. This usually entails a degree of finger fracture through uninjured liver, which allows visualization of the bleeding raw surface and more direct control. Application of specific liver clamps, such as the Lin clamp, designed to aid in lobectomy, is difficult because of positioning of the injury laceration and maneuvering around the clamp.

Being able to perform a tractotomy of a missile wound should be in a surgeon’s armamentarium when dealing with penetrating hepatic injury. In addition, a variety of methods designed for tamponade of the bleeding missile tract have been described, using various materials. Bluett et al. described a tamponade device with multiple Penrose drains dragged through the liver tract. However, it is preferable to open the liver and suture or clip-control the bleeding site directly if possible.

Once the bleeding has been controlled, the large, raw surface of the liver can be problematic, as persistent oozing of bile or blood continues. A viable omental patch sutured to the liver bed is an excellent homeostatic agent and internal drain. Stone and Lamb popularized the omental pack in their initial report. Fabian and Stone reported 90% successful hemostatic control with this procedure. For large, raw liver surfaces resulting from debridement or tractotomy, the omental patch held in place with several liver sutures is an excellent hemostatic agent. Utilization of the argon beam coagulator is another option for addressing bleeding of raw liver surfaces. The argon gas removes the blood from the hepatic tissue, and ionizing energy is transmitted. A maximum of 110°C is achieved and an eschar is formed.

An alternative to surgical repair of the injured liver is a mesh wrap
intended to provide compression, control bleeding, and close parenchymal defects. Delaney et al.\textsuperscript{68} reported success in six liver injuries controlled in this manner. Brunet et al.\textsuperscript{69} reported 35 liver injuries wrapped for control. Sequential CT examination of the patients demonstrated progressive restoration of normal liver architecture.

The premise underlying much of the preceding discussion is that liver bleeding can be controlled. However, even when advanced techniques of liver control are used, hemorrhage control can be precarious at best. A critical error that can be made when dealing with major liver injury is to continue operative intervention in the face of a hypothermic (less than 32°C), acidotic patient who has developed coagulopathy. Although the specific time to make a decision to pack the liver and restore normothermia and coagulation factors is not always clear, the operating surgeon should always have a low threshold to incorporate packing and prepare the patient to be expeditiously transferred to the intensive care unit for aggressive resuscitation and monitoring. Once a patient has required a 10-U transfusion, packing should be seriously considered. Garrison et al.,\textsuperscript{70} in a review in which they tried to predict the need for packing in severe abdominal injuries, noted that patients with severe injuries, hypothermia, refractory hypertension, coagulopathy, and acidosis need early packing. It needs to be emphasized that large-vessel bleeding must be controlled before packing can be effective.

Perihepatic packing was popularized during World War II. The high incidence of complications, plus the advent of more sophisticated techniques for control of liver bleeding, led to the demise of packing until its revival in the 1970s. Feliciano et al.\textsuperscript{71} noted the major indications for perihepatic packing to be the postrepair coagulopathy that developed or an extensive subcapsular hematoma or capsular avulsion. They reported 57% survival rate in their series. Carmona et al.\textsuperscript{72} reported similar success with perihepatic packing to control bleeding when other methods failed. Perihepatic packing is broadly embraced today. It is also a valuable adjunct to resectional debridement and tractotomy. Walt\textsuperscript{73} has enumerated several guidelines regarding liver packing. The use of a folded, disposable plastic drape is helpful. It is placed against the liver and the packs placed on it, preventing the laparotomy pads from adhering to the liver and possibly minimizing the recurrent bleeding upon removal of the packs. Gauze packs are then placed in order to compress the liver. The packs should be placed at both the superior
and inferior surfaces of the liver. The packing should be tight enough to control the bleeding but not so tight that it unnecessarily compresses the renal vessels and possibly the inferior vena cava, resulting in intra-abdominal hypertension. Patients who have undergone packing will require continued sedation with mechanical ventilation until pack removal, because of the interference of optimal diaphragmatic movement. Abdominal wall closure is rapid and is performed by towel clips or by running nylon suture in the skin. Utilization of silo-like closures with sterile towels and plastic drapes should be used to minimize fluid loss and maintain abdominal pressure. In addition, there should always be a high index of suspicion for the development of intra-abdominal compartment syndrome.

Pack removal can be planned when the patient has regained normothermia and coagulation parameters have been normalized. This usually occurs within 24 to 72 hours. Packs are then removed during a second operation, and the surgical team again must be prepared to manage bleeding. Repacking at the second operation might be indicated. The complication rate of packing is appreciable. Ivatury et al. noted an increased incidence of sepsis in a group of patients subjected to liver packing. An additional benefit of liver packing is that it may allow transport of a critically ill patient from one center to a definitive treatment center where the liver injury can be treated. Clark et al. emphasized this point in the context of a trauma system, with a number of smaller, more rural hospitals transporting seriously injured patients to the tertiary center for definitive care.

**JUXTAHEPATIC VENOUS INJURIES**

The lethality of juxtahepatic venous injuries in blunt hepatic trauma and the management challenges of definitively addressing such injuries have been well chronicled. Fortunately, such liver wounds are seen infrequently. However, the downside is that very few acute care surgeons are familiar with and comfortable operating in this specific setting. Depending on the particular series, the mortality ranges from 50% to 80%, with massive hemorrhage being the overwhelming cause of death.

The deadly nature of this injury is a result of the difficulty in expeditiously getting access to the injury site. The retrohepatic vena cava and major hepatic veins are within the depth of the least mobile area of the liver—making exposure and direct control of bleeding very challenging. Attempting to
rotate the liver in an effort to access the injury can actually extend the wound and cause increased bleeding. Also, such a misguided effort could result in a fatal air embolus.

Detailed knowledge of the pertinent anatomy is imperative for any surgeon attempting an operative management strategy. The juxtahepatic vena cava, which is within the “bare area” of the liver, extends for approximately 7 cm and is bordered by the phrenic veins and right adrenal vein—cephalad and caudad, respectively. Approximately 3 cm above the most superior aspect of the retrohepatic vena cava, the inferior vena cava enters the right atrium. The retrohepatic cava is an extraparenchymal structure. The three major hepatic veins, along with their tributaries, enter directly into the anterior aspect of the retrohepatic vena cava. This anatomy is relatively constant, with major anomalies being uncommon. While the course of the extraparenchymal hepatic veins is short, the intraparenchymal veins have a long course. Substantial blunt trauma can lacerate/avulse either or both.

Probably because of their highly lethal nature, juxtahepatic venous injuries are infrequently managed. Surrounding structures can provide a tamponade effect and contain juxtahepatic venous hemorrhage. Such structures include the liver, the diaphragm, and the suspensory ligaments of the liver. Adequate containment of hemorrhage by these structures might allow an attempt at expectant or nonoperative management. However, if these supporting structures are disrupted, substantial bleeding will ensue. As a consequence, overly aggressive or injudicious hepatic mobilization can result in uncontrollable hemorrhage.

Juxtahepatic injuries, which can be caused by blunt or penetrating injuries, are often classified as type A or B, with the former being hepatic venous wounds that are intraparenchymal and the latter being extraparenchymal venous wounds. Both type A and B injuries can occur together. In addition, there can be associated injuries to the portal vein and its tributaries, which occur more frequently with type A wounds. Fortunately, the extraparenchymal hepatic venous or the associated retrohepatic caval injuries are infrequent. Penetrating wounds to this anatomic region or the sheer forces from blunt injury are the predominant mechanisms of injury. Irrespective of the reported series on the management of juxtahepatic venous injuries, the mortality rates are overwhelmingly high.

There are basically three operative approaches in the management of juxtahepatic venous injuries: (1) direct repair of the venous wound(s), (2)
surgical resection, and (3) pressure application (containment/tamponade measures) with reinforcement of the natural containment structures that have been disrupted. While there have been several reports of the specific strategy and efficacy of operative exposure and direct repair of juxtahepatic venous injuries, the success is sporadic and overall outcomes dismal.  

In 1966, Feldman was credited with reporting the first successful application of direct suture repair of a juxtahepatic venous injury. Schrock introduced, in 1968, the concept of vascular isolation with the utilization of an atrio caval shunt (Fig. 19-4). However, the majority of surgeons have abandoned atrio caval shunting because of the challenges related to the technique and the overall dismal outcomes. The paramount or overarching principle in establishing vascular isolation is obtaining proximal and distal control of all vessels to totally isolate the liver. The Heaney maneuver advocates a more expedient approach to achieve vascular isolation (Fig. 19-5) to surgically address juxtahepatic venous injuries and other complex liver wounds. At all times, it is imperative that the patient is optimally resuscitated and closely monitored. Another alternative, with respect to achieving vascular isolation in an effort to access retrohepatic wounds, is the establishment of a venovenous bypass (Fig. 19-6). This approach necessitates cannulation of the femoral vein and the axillary vein in the upper arm. The cannulas are connected by a heparin-coated tubing, with a flow assisted by a centrifugal pump. Both supra- and intrahepatic clamps are required for the venovenous bypass. Along with inexperience in the above techniques, major blood loss with associated coagulopathy precludes successful utilization of any of the shunting interventions. Operative hepatic resection in an effort to access these retrohepatic wounds is associated with a high mortality rate and should not be attempted.
FIGURE 19-5 The Heaney maneuver. Vascular isolation of the injured liver by applying vascular clamps to the suprahepatic and infrahepatic inferior vena cava, in addition to a Pringle maneuver.
Because of the inherent and overwhelming risks of surgical management of these complex injuries, tamponade with containment followed by angiography and possible embolization has become a viable option (when possible) in the management of juxtahepatic venous injuries. Such an approach often requires temporarily leaving the abdomen open. Although omentum has been proposed to create the tamponade effect, gauze packing is more expedient and effective. Pachter et al. described a “nonshunting approach” which consists of four components: (1) manual compression and aggressive fluid resuscitation; (2) prolonged portal triad occlusion (mean occlusion time, 46 min); (3) rapid and extensive finger fracture for vascular control, almost always through normal hepatic parenchyma to the site of injury; and (4) wide mobilization of the hepatic attachments with medial rotation of the liver to provide access to both the retrohepatic cava and the hepatic vein. In their series, six of the nine “nonshunted” patients survived.

PORTA HEPATIS
Injuries to the porta hepatis are rare, usually complex, and highly lethal. Review of the literature showed three large series that cumulatively report 180 patients treated between 1965 and 1994. These injuries are usually penetrating, occurring in 50% to 100% of the populations reported. Isolated injuries to the portal structures occur and are far more survivable than are multiple injuries. Overwhelming hemorrhage is the usual cause of death in all reported series.

The porta hepatis is composed of the hepatic artery, extrahepatic bile duct system, and the portal vein. The proximity of these structures to other major structures, and their relatively difficult exposure, explains their high lethality. In the multi-institutional survey compiled by the Western Trauma Association and reported by Jurkovich et al., an overall 51% mortality rate was recorded. When broken down, the morality rate in single-structure injuries is still 45%, whereas the mortality rate in multiple-structure injuries rises to 80%. This is in line with results in other reports in the literature.

**PORTAL VEIN**

Injuries to the portal vein are responsible for most deaths ascribed to portal structures. Once identified and the bleeding controlled, the question of repair versus ligation must be addressed. Ligation of the portal vein can be tolerated, in that there will be decompression of the portal hypertension by collateral vessels. Unfortunately, in patients subjected to ligation of the portal vein, the mortality rate is as high as 90%. This is in disagreement with survival rates of 50% to 80% reported previously by Pachter et al. and Stone et al. Patients treated by ligation of the portal vein have greater circumferential disruption of the vein and overwhelming hemorrhage, and ligation is used as a rapid method of bleeding control. Repair of the portal vein is used with lesser degrees of injury—in circumferential injury less than 25%—and is reported to have increased survivability. Many of the deaths occur because of massive hemorrhage before a repair can be accomplished. When confronted with a portal venous injury, repair is preferable to ligation, although ligation is an acceptable option. Second-look laparotomy to check for bowel viability has been advocated when the portal vein has been ligated.

**HEPATIC ARTERY**
The liver receives a dual blood supply from the hepatic artery and the portal vein, allowing ligation of the hepatic artery without absolutely compromising hepatic blood supply. Lobar artery ligation is well tolerated, but overall mortality rate remains in excess of 40%.

EXTRAHEPATIC BILIARY DUCTS

Bile duct injuries are uncommon, even in this relatively uncommon injury cluster. Partial circumferential disruption can be treated by primary repair as well, as demonstrated from experience with iatrogenic bile duct injury at the time of cholecystectomy. Complex or complete disruption of the ductal tree is best managed by biliary-enteric anastomosis. End-to-end anastomosis has an excessive stenosis rate. Adequate drainage of the area is essential, because bile leaks can occur. On rare occasions, stenting and external drainage have been used in an unstable patient, with biliary reconstruction accomplished at a later date.\textsuperscript{87}

The key to the diagnosis of bile duct injury is suspicion that the injury has occurred. Evidence of bile staining and the presence of a duodenal injury should prompt investigation that is best done by an intraoperative cholangiogram. Small injuries may be missed at initial exploration. Endoscopic retrograde cholangiopancreatogram with stenting may provide diagnostic therapeutic answers if a patient develops a biloma subsequent to a missed injury.

Once patients with operative hepatobiliary trauma sustain surgical hemostasis, they may become hypothermic and coagulopathic with bleeding occurring from nonsurgical sources, in particular the raw liver parenchyma. At this point, the liver and other sources of nonsurgical bleeding may be packed with laparotomy pads and a temporary abdominal closure performed.\textsuperscript{88–94} Patients can then be transported to the intensive care unit where they may be further resuscitated and warmed. Take-back for removal of the packing and debridement of devitalized liver may generally be undertaken safely in 24 to 48 hours. Omental packing of the liver defect originally described by Stone may reduce the incidence of bile leak and abscess formation.\textsuperscript{95}

SPECIFIC CONSIDERATIONS FOR PENETRATING
ABDOMINAL TRAUMA

The evolution in the management of penetrating abdominal trauma parallels the evolution of diagnostic modalities. In the 19th century, expectant (observation) management was the approach of choice worldwide. In the 1880s, Paule Reclese, a French surgeon, advocated supportive care only for penetrating abdominal injuries. Sir William McCormick, chief Army Surgeon during this same period, coined the McCormick aphorism regarding the management of gunshot wounds to the abdomen that stated “if a man undergoes surgery after being shot he dies and lives if left in peace.” Even with a mortality rate that was exceedingly high, such dogma was the standard of care during this era for any penetrating abdominal trauma. With predictably overwhelming morbidity/mortality associated with these injuries, it became apparent that a more aggressive, interventional approach was needed for penetrating injuries to the abdomen, and as a result, mandatory exploration, or celiotomy, became the prevailing management option of choice and essentially the standard of care.

Shafter and Nance’s landmark articles, which emphasized surgical judgment in the management of penetrating wounds of the abdomen, changed the approach to penetrating abdominal injuries from mandatory celiotomy to a more selective management.\textsuperscript{96,97} Enhanced diagnostic imaging has greatly assisted in making the nonoperative/selective management a more reliable and acceptable treatment option in penetrating abdominal trauma.

Topography and Clinical Anatomy

The abdomen is often defined as a component of the torso that has for its superior boundary the left and right hemidiaphragm, which can ascend to the level of the nipples (4th intercostal space) on the frontal aspect and to the tip of the scapula in the back. The inferior boundary of the abdomen is the pelvic floor. For clinical purposes, it is helpful to further divide the abdomen into four areas: (1) anterior abdomen (below the anterior costal margins to above the inguinal ligaments and anterior to the anterior axillary lines), (2) intrathoracic abdomen (from the nipple or the tips of the scapula to the inferior costal margins), (3) flank (inferior scapular tip to the iliac crest and between the posterior and anterior axillary lines), and (4) back (below the tips of the scapula to the iliac crest and between the posterior axillary lines). The
majority of the digestive system and urinary tract, along with a substantial
network of vasculature and nerves, are contained with the abdominal cavity.
A viscer-a-rich region, the abdomen can often be the harbinger for occult
injuries as a result of penetrating wounds, particularly in the unevaluable
abdomen as a result of a patient’s compromised sensorium.

**Mechanism of Injury**

In addition to the hemodynamic status of the patient, important variables in
the decision-making regarding management of penetrating abdominal injuries
are the mechanism and location of injury. The kinetic energy generated by
hand-driven weapons, such as knives and sharp objects, is substantially less
than that caused by firearms. Although not always evident, it is important to
know the length and width of the wound along with the depth of penetration
of the weapon or device that caused the stab injury. For example, a stab
injury usually results in a long, more shallow wound that does not penetrate
the peritoneum. Local wound management is the primary focus for these
injuries with no concern for any potential intra-abdominal injury.\(^98\) Although
some stab wounds do not penetrate the peritoneal cavity, such cannot be
assumed without some formal determination or serial abdominal
examinations to assess for worsening abdominal tenderness or the
development of peritoneal signs.

There is notable variability among the full spectrum of firearms in the
civilian setting, with this arsenal including mostly handguns, rifles, shotguns,
and airguns. The kinetic energy, which correlates with the wounding
potential, is dependent on mass and velocity (\(KE = 1/2 \text{ mr}^2\)). Therefore, the
higher the velocity, the greater the wounding potential.\(^99\) Because the barrel
is longer in a rifle than a handgun, the bullet has more time to accelerate—
generating a much higher velocity. A high velocity missile is propelled at
2500 feet/second or greater. Airguns usually fire pellets (eg, BBs) and are
associated with a lower velocity and wounding potential. Shotguns fire a
cluster of metal pellets, called *shot*. The pellets separate after leaving the
barrel, with a rapidly decreasing velocity. At a distance, the wounding
potential is diminished. However, at close range (less than 15 feet), because
of the increase in aggregate mass, the tissue destruction is similar to a high-
velocity missile injury.
Although each injury should be handled on an individual basis, there are general principles that will provide some guidance in the management of penetrating injuries based on mechanism of injury. With respect to stab wounds, approximately one-third of the wounds do not penetrate the peritoneum, and only half of those that do penetrate require operative intervention. The number of organs injured and the intra-abdominal sepsis complication rate are significantly less than wounds caused by gunshots.\textsuperscript{100,101}

**Physical Examination**

A complete and thorough physical examination of the entire body is essential in the management of penetrating abdominal injury. There are some findings (Table 19-10) on physical examination that are absolute indications for operative intervention. The components of the physical exam should include careful inspection, palpation, and auscultation.

<table>
<thead>
<tr>
<th>TABLE 19-10: ABSOLUTE INDICATIONS FOR EXPLORATORY LAPAROTOMY IN PENETRATING ABDOMINAL INJURIES</th>
</tr>
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<tbody>
<tr>
<td>A. Peritonitis</td>
</tr>
<tr>
<td>B. Evisceration</td>
</tr>
<tr>
<td>C. Impaled object</td>
</tr>
<tr>
<td>D. Hemodynamic instability</td>
</tr>
<tr>
<td>E. Associated bleeding from natural orifice</td>
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<tr>
<td>F. Documented pneumoperitoneum</td>
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In addition to being able to determine the location, extent, and the number of wounds, inspection can sometimes determine the trajectory of the missile or other wounding agent, and consequently guide management decisions. For example, a patient with a documented, superficial tangential gunshot wound (low-velocity) with no other remarkable physical findings would likely be managed expectantly (observation). However, if a penetrating abdominal injury results in a patient presenting with an evisceration, exploratory laparotomy would be the management option of choice. Palpation will enable
the examiner to elicit abdominal tenderness or frank peritoneal signs, along with being able to detect abdominal distention and rigidity. On occasion, missiles can be palpated lodged in the soft tissue. Unless in a controlled and sterile setting such as the operative theater, probing of a wound should be avoided. Auscultation is also an important component of the physical examination. It can help determine diminished or absent bowel sounds that could be suggestive of evolving peritonitis. Also, auscultation could detect a trauma-induced bruit, suggestive of a vascular injury.

The examiner has to be keenly aware of the fact that there are situations in which the abdominal exam will be unreliable due to possible spinal cord injury or a patient’s altered mental state.

**Diagnostic Studies**

Even with penetrating injuries, the abdomen is notorious for hiding its secrets—occult injuries. Access to an extensive diagnostic armamentarium is imperative in the optimal management of these injuries. Strongly advocated by some for abdominal stab wounds, local wound exploration has the advantage of allowing the patient to be discharged from the trauma bay or emergency department if surgical exploration of the wound fails to demonstrate penetration of the posterior fascia and peritoneum. However, if the patient has to go to the operating room for other injuries, the local wound exploration should be done in the surgical suite, which will have better lighting and a more sterile environment. A positive finding during local wound exploration dictates a formal laparotomy or laparoscopy. However, even with local wound exploration as a guide, the nontherapeutic laparotomy rate can be high, given that only one-third of the patients with stab wounds to the anterior abdomen require therapeutic laparotomies.\textsuperscript{102,103} In the patient who has an evaluable abdomen, serial abdominal examinations would be an acceptable alternative to local wound exploration in order to determine the need for operative intervention. Local wound exploration should only be done for stab wounds to the anterior abdomen. Such an approach is potentially too hazardous for thoracoabdominal penetrating injuries and back/flank wounds. Plain radiography (abdomen/pelvis/chest) can be pivotal in documenting the presence of missiles and other foreign bodies and determining the trajectory of the injury tract, particularly for wounds from firearms. Also, the presence of free air might be confirmed by plain radiography. Unless there is concern
about a retained broken blade, there is little utility for plain radiography for stab injuries.\textsuperscript{104} DPL has never had a broad appeal in the diagnostic evaluation of penetrating abdominal wounds. Although some have advocated its use with tangential wounds of the abdominal wall, the technique has failed to receive widespread support.\textsuperscript{105} Its reliability in detecting clinically significant injuries sustained as a result of penetrating abdominal injuries has been an ongoing concern.\textsuperscript{106–108} The reported sensitivity and specificity of DPL for abdominal stab wounds are 59\% to 96\% and 78\% to 98\%, respectively.\textsuperscript{109} Also, DPL is a poor diagnostic modality for detecting diaphragmatic and retroperitoneal injuries.

As with blunt trauma, diagnostic imaging has had the greatest impact in changing the face of trauma management, with CT taking the lead in this area. Its ubiquitous presence in the management of blunt abdominal trauma has been underscored. However, it is becoming an important diagnostic study in the evaluation of penetrating abdominal injuries. In addition to its excellent sensitivity in detecting a pneumoperitoneum, free fluid, and abdominal wall/peritoneal penetration, CT is helpful in identifying the tract of the penetrating agent. Hauser et al. recommended the use of “triple contrast” CT in the assessment of penetrating back and flank injuries.\textsuperscript{110} CT scan evaluation is an essential diagnostic tool in the increasing advocacy for selective management of abdominal gunshot wounds obviating the need for mandatory surgical exploration.\textsuperscript{111} However, there still remain two major limitations of CT: detection of an intestinal perforation and a diaphragmatic injury.

Unless the injury is confined to the solid organ of the abdomen, such as the liver or spleen, the matrix of intestinal gas patterns makes detection of penetrating injuries difficult. Kristensen, Buemann, and Kuhl were one of the first teams to introduce the role of ultrasonic scanning as part of the diagnostic armamentarium in trauma management.\textsuperscript{112} Kimura and Otsuka endorsed using ultrasonography in the emergency room for evaluation of hemoperitoneum.\textsuperscript{113} FAST does not have the same broad application in the evaluation of penetrating trauma as it does in blunt trauma assessment. Rozycki et al. reported on the expanded role of ultrasonography as the “primary adjuvant modality” for the injured patient assessment.\textsuperscript{114} Rozycki also reported that FAST examination was the most accurate for detecting fluid within the pericardial sac. Such a finding would be confirmatory for a
possible cardiac injury and potential or existing cardiac tamponade, given a mechanism of injury that could result in a traumatic cardiac injury.

As a diagnostic modality, laparoscopy has been used by other specialists for several decades. However, it was formally introduced as a possible diagnostic procedure of choice for specific torso wounds when Ivatury et al. did a critical evaluation of laparoscopy on penetrating abdominal trauma.\textsuperscript{115} Fabian et al. also reported on the efficacy of diagnostic laparoscopy in a prospective analysis.\textsuperscript{116}

With there no conventional diagnostic tool that can conclusively rule out a diaphragmatic laceration or rent, diagnostic laparoscopy becomes the study of choice for penetrating thoracoabdominal injuries, particularly left thoracoabdominal wounds (Fig.19-7). Laparoscopy can also be used to determine peritoneal entry from a tangential penetrating injury.

![Flowchart](image)

**FIGURE 19-7** Management algorithm for penetrating thoracoabdominal injuries.

\*Operative intervention is mandatory for all high-velocity injuries, irrespective of left or right.
Penetrating Abdominal Injuries and the Hemodynamically Stable and Unstable Patient

As highlighted above, the management principles in patients who sustain penetrating abdominal injuries and remain hemodynamically stable depend on the mechanism and location of injury along with the hemodynamic status of the patient. Irrespective of the patient’s hemodynamic parameters, the ATLS protocol should be strictly followed upon arrival of the patient to the trauma bay.  

Trauma Laparotomy

The operative theater should be large enough to accommodate more than one surgical team in the event the patient might require simultaneous procedures to be performed. In addition, the room should have the capability of maintaining room temperature as high as the lower 80s F plus range in order to avoid having a hypothermic patient. There should be a rapid transfusion device in the room to facilitate the delivery of large fluid volume and ensure that the fluid administration is appropriately warm.

Abdominal exploration for trauma has basically four imperatives: (1) hemorrhage control, (2) contamination control, (3) identification of the specific injury(ies), and (4) repair/reconstruction. The abdomen is prepared with a topical antimicrobial from sternal notch to bilateral mid-thighs and extending the prep laterally to the side of the operating room table, followed by widely draping the patient. Such preparation allows for expeditious entry into the thorax if needed and possible vascular access or harvesting. Exploration is initiated with a midline vertical incision that should extend from the xyphoid to the symphysis pubis in order to achieve optimal exposure.

The first priority upon entering the abdomen is control of exsanguinating hemorrhage. Such control can usually be achieved by direct control of the lacerated site or obtaining proximal vascular control. After major hemorrhage is controlled, blood and blood clots are removed. Abdominal packs (radiologically labeled) are used to tamponade any bleeding and allow for identification of any injury bleeding. The preferred approach to packing is to divide the falciform ligament and retract the arterial abdominal wall. This
will allow manual placement of the packs above the liver. Abdominal packs should also be placed below the liver. This arrangement of the packs on the liver creates a compressive tamponade effect. After manually eviscerating the small bowel out of the cavity, packs should be placed on the remaining three quadrants, with care taken to avoid any iatrogenic injury, especially to the spleen. During the packing phase after ongoing hemorrhage has been controlled, the surgeon should communicate with the anesthesia team that major hemorrhage has been controlled and that this would be an optimal time to establish a resuscitative advantage with fluid/blood/blood product administration.

The next priority should be control or containment of gross contamination. This begins with the removal of the packs from each quadrant—one quadrant at a time. Packs should be removed from the quadrants that you least suspect to be the source for blood loss, followed by removal of the packs from the final quadrant—the one that you believe is the area of concern.

After control of major hemorrhage has been achieved, any evidence of gross contamination must be addressed immediately. Obvious leakage from intestinal injury can be initially controlled with clamps (eg, Babcock clamp), staples, or sutures. The entire abdominal gastrointestinal tract needs to be inspected, including the mesenteric and antimesenteric border of the small and large bowel, along with the entire mesentery. Rents in the diaphragm should also be closed to prevent contamination of the thoracic cavity.

Further identification of any and all intra-abdominal injuries should be initiated. Depending on the mechanism of injury and the estimated trajectory of wounding agent, a thorough and meticulous abdominal exploration should be performed, including entering the lesser sac to better inspect the pancreas and the associated vasculature. In addition, mobilization of the C-loop of the duodenum (Kocher maneuver) might be required, along with medical rotation of the left and/or right colon for exposure of vital retroperitoneal structures.

The final component of a trauma laparotomy is definitive repair, if possible, of specific injuries. The status of the patient dictates whether each of the components of a trauma laparotomy can be achieved at the index operation. A staged celiotomy (“damage control” laparotomy) might be necessary if the patient becomes acidotic, hypothermic, develops coagulopathy, or is hemodynamically compromised.
Definitive Management of Specific Injuries

SMALL INTESTINES

Isolated small bowel enterotomies can be closed primarily with nonabsorbable sutures for a one-layer closure. If the edges of the enterotomy appear nonviable they should be gently debrided prior to primary closure. However, multiple contiguous small bowel holes or an intestinal injury on the mesenteric border with associated mesenteric hematoma will likely necessitate segmental resection and anastomosis of the remaining viable segments of the small bowel. The operative goal is always the reestablishment of intestinal continuity without substantial narrowing of the intestinal lumen, along with closure of any associated mesenteric defeat. Application of non-crushing bowel clamps can contain ongoing contamination while the repair is being performed. Although a hand-sewn or stapler-assisted anastomosis is operator dependent, trauma laparotomies are time-sensitive interventions and expeditious management is imperative.

COLON

The segment of injured bowel should be thoroughly inspected, particularly missile injuries that are most common—through-and-through enterotomies. This requires adequate mobilization of the colon in order to visualize the entire circumference of the bowel wall. Initially controversial, an enterotomy (right- or left-sided injuries) of the colon can be closed primarily, irrespective of contamination or transient shock state. If the colon injury is so extensive that primary repair is not possible or would severely compromise the lumen, a segmental resection should be performed. Depending on the environmental setting, the remaining proximal segment can be anastomosed to the distal segment, or a proximal ostomy and Hartmann procedure can be performed. If the distal segment is long enough, a mucous fistula should be established. Documented rectal injuries below the peritoneal reflection should necessitate constructing a diverting colostomy and presacral drainage (exiting from the perineum). Such drainage is, however, not universally endorsed.

STOMACH/DUODENUM

With respect to penetrating wounds of the stomach, the anterior and posterior
aspects of the stomach need to be meticulously inspected for accompanying through-and-through injuries. Penetrating injuries of the stomach should be repaired primarily after debridement of nonviable edges. The primary repair can either be performed in a single layer with nonabsorbable suture or as a double-layer closure with an absorbable suture (eg, Vicryl) for the first layer, the second layer being closed with nonabsorbable sutures (eg, silk). There are very few penetrating injuries of the stomach that would compromise the gastric lumen. Also, it is unlikely that primary repair of a through-and-through stomach injury would compromise the gastric lumen. Duodenal injuries can be repaired primarily in a one- or two-layered fashion if the penetration is less than half the circumference of the duodenum. However, for more complex duodenal injuries, an operative procedure is needed to divert gastric contents away from the site (where closure of the wound has been attempted). Performing a pyloric exclusion with the establishment of a gastrojejunostomy is such a procedure.\textsuperscript{119–121}

**PANCREAS**

Superficial or tangential penetrating wounds of the pancreas in which there is not an injury to the main pancreatic duct can be externally drained. However, a penetrating injury that transects the pancreas, including the main pancreatic duct, requires extirpation of the distal pancreas (distal pancreatectomy), particularly if the transection site is to the left of the superior mesenteric vessels. A more proximal penetrating injury that involves the main pancreatic duct, with associated complex duodenal injury (eg, injury to the ampulla), would likely necessitate a pancreateoduodenectomy. Unfortunately, because of the rich vascular network surrounding the pancreas, penetrating pancreatic wounds can be lethal injuries.

**SPLEEN**

Most penetrating splenic injuries, particularly gunshot wounds, require a splenectomy. In order to visualize the entire spleen, it should be mobilized to the midline by dividing its ligamentous attachments. Superficial penetrating injuries of the spleen can sometimes be managed by either splenorrhaphy or application of a topical hemostatic agent. Splenorrhaphy can be done by a pledgeted repair or an omental buttress. However, complex repair of the
spleen is not a prudent approach in the always time-sensitive trauma setting.

GALLBLADDER AND LIVER

Penetrating injuries to the gallbladder dictate the need for extirpation. There is no role for primary repair of a penetrating wound to the gallbladder.

Liver injuries are common in both blunt and penetrating trauma. The majority of injuries are superficial or minor and require no surgical repair. Simple application of pressure and/or a hemostatic agent or fibrin glue will constitute definitive management of the majority of these injuries. The argon beam coagulator, also a helpful adjunct in superficial hepatic injuries with persistent oozing, generates ionizing energy through an argon gas stream that causes rapid coagulation. The operative armamentarium for complex penetrating hepatic injuries is highlighted in Table 19-11.

TABLE 19-11: CONSIDERATIONS FOR HEPATIC INJURY

- Portal triad occlusion (Pringle maneuver)
- Hepatic artery ligation
- Hepatotomy (sharp or finger fracture with distal vein isolation)
- Resectional debridement
- Omental buttress
- Intrahepatic balloon tamponade
- Atrial caval shunt (to the superior vena cava)
- Abdominal packing

GENITOURINARY SYSTEM

Less than 10% of patients with penetrating abdominal wounds sustain genitourinary tract injuries. The majority of the injuries are renal. Penetrating injuries that result in a grade IV (cortical/calyceal injury and associated vascular injury with contained hemorrhage) or grade V (shattered kidney and vascular avulsion) invariably necessitate a nephrectomy, particularly if there is a viable contralateral kidney. Lacerations or more superficial wounds of the kidney might require renorrhaphy, with approximation of the disrupted
capsule with pledgeted sutures or a prosthetic (mesh) wrap. Absorbable interrupted suture should be used, and all repairs should be drained. The injury pattern might dictate the need for a partial nephrectomy. Ureteral injuries can be extremely difficult to identify in penetrating wounds with an accompanying retroperitoneal hematoma. When possible, the ureter should be repaired primarily with interrupted absorbable suture over a double J stent. A complete transection of the ureter requires debridement of the nonviable edges, spatulation of the ends, and primary repair over a stent. All repair sites should be adequately drained. If the anastomosis cannot be performed in a tension-free fashion, a bladder flap (Boari) could be surgically constructed, with implantation of the proximal segment of the transected ureter into the flap. A psoas “hitch” might be required if there is any tension on the flap and the tunneled ureter.

Penetrating injury to the intraperitoneal bladder requires surgical repair. After confirming that there is no involvement of the trigone, the bladder should be closed with a two-layer closure with absorbable suture (the second layer incorporates Lembert sutures to imbricate the first layer). Suprapubic drainage should only be done selectively; however, a Foley catheter should be left in place.

**Retroperitoneal Hematomas**

The retroperitoneum, an organ-rich region, has several vital structures that can be injured when its boundaries are penetrated. It can be a major potential site for hemorrhage in patients sustaining either penetrating or blunt trauma, due to the substantial vascularity along with bleeding that can occur from an associated solid organ wound (eg, kidney). In the central region (Zone 1) of the retroperitoneum resides the abdominal aorta, celiac axis, and the superior mesenteric artery, vena cava, and proximal renal vasculature. The lateral retroperitoneum (Zone 2) encompasses the proximal genitourinary system and its vasculature. The pelvic retroperitoneum (Zone 3) contains the iliac arteries, veins, and their tributaries. In addition to the vasculature and the kidneys (plus ureters), the retroperitoneum contains the second, third, and fourth portion of the duodenum, along with the pancreas, the adrenals, and the infrapelvic portion of the colon and rectum. Table 19-12 underscores the management principles of trauma-related retroperitoneal hematomas. Ideally, proximal (and when applicable, distal) control needs to be achieved prior to
exploring any retroperitoneal hematoma. For retroperitoneal hematomas in Zone I, irrespective of a penetrating or blunt mechanism, mandatory exploration is required. Also, retroperitoneal hematoma in any of the three zones requires exploration for all penetrating injuries. For Zone II retroperitoneal hematomas resulting from blunt trauma, all pulsatile or expanding hematomas should undergo exploration. Gross extravasation of urine also necessitates exploration. Zone III (pelvic retroperitoneum) hematomas should be explored only for penetrating injuries to determine if there is a specific intrapelvic colorectal, ureteral, or vascular injury. However, such an approach should not be taken for blunt trauma, as the injury would likely be venous, and application of an external compression device would be the preferred intervention. An arterial injury could be addressed by arteriography/embolization.

### TABLE 19-12: RETROPERITONEAL HEMATOMAS

<table>
<thead>
<tr>
<th>Zone I</th>
<th>Zone II</th>
<th>Zone III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating</td>
<td>Explore</td>
<td>Explore</td>
</tr>
<tr>
<td>Blunt</td>
<td>(Not mandatory)</td>
<td>Explore</td>
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<tr>
<td></td>
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### SPECIAL INTERVENTIONS

**Intra-Abdominal Packing and “Damage Control” Strategy**

“Damage control” strategy, popularized by Rotondo et al., is a staged celiotomy strategy that was initially made operationally viable by Mattoo and Feliciano and labeled the “Bogota bag” approach. Although this approach was not actually developed by them, Mattoo and Feliciano popularized the technique and made it acceptable for use in this country.\(^{122–126}\) Regardless of the name given to this strategy of surgically managing only immediate life-threatening injuries (along with intra-abdominal packing and rapid temporary closure of the abdominal cavity), the goal is the same—avoiding the potential irreversibility of sustained acidosis, hypothermia, coagulopathy, and
hemodynamic lability by delaying definitive operative management until the patient can be stabilized in the intensive care unit. Although “damage control” is most frequently used in association with severe hepatic wounds, other organ injuries, including vascular wounds, can necessitate this staged celiotomy approach with hepatic packing and a rapid, creative abdominal closure.

Resuscitative Endovascular Balloon Occlusion of the Aorta

Bleeding remains the leading cause of preventable death in trauma patients that reach the hospital.\textsuperscript{127} Both penetrating and blunt trauma can lead to life-threatening injury of the abdominal vasculature. Traumatic injury to vessels may occur via direct laceration and transection or blunt injury resulting in dissection or thrombosis. While endovascular treatment of abdominal vascular injuries has become increasingly utilized, the unstable patient with active hemorrhage will still require open surgical intervention.\textsuperscript{128} Appropriate management of these patients centers on prompt recognition of the injury, rapid exposure, and control of hemorrhage. Prior to operative intervention, the use of permissive hypotension has been shown to improve survival and decrease hospital stay. The goal of permissive hypotension is to maintain perfusion to the vital organs while decreasing the amount of hemorrhage and clot disruption at the site of injury. Improved outcomes are thought to be due to the improved thrombus formation at the site of injury as well as a decrease in both dilutional and consumptive coagulopathy.\textsuperscript{129} Despite advances in technology, mortality from abdominal vascular injury remains high, with mortality from penetrating injuries to the abdominal aorta approaching 80%.\textsuperscript{130} Survival of these patients hinges on rapid exposure and control of the hemorrhage. Operative exposure of abdominal vasculature and surgical repair is described in detail \textit{Chapter 20}, Abdominal Vascular Emergencies. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is gaining popularity as an adjunct for controlling major intra-abdominal hemorrhage. The technique was first described in 1953 during the Korean War by Dr. Lieutenant Colonel David Hughes on three soldiers in hemorrhagic shock. The surgeon placed a Foley through the femoral artery to provide proximal vascular control. Although none of the three patients
survived, Hughes noted temporary improvement with inflation of the balloon. However, the procedure was not widely adopted during this time, likely due to concerns regarding the technical difficulty of the procedure and availability of the equipment needed. In 2000, Greenberg and colleagues first described the use of an aortic balloon occlusion device to control hemorrhage prior to endovascular repair for ruptured abdominal aortic aneurysms in three patients. As the use of REBOA has continued to increase in the field of vascular surgery, it has also recently gained momentum as an effective method of obtaining proximal control in the setting of life threatening abdominal or pelvic trauma.

REBOA is currently indicated for refractory hemorrhagic shock due to abdominal or pelvic trauma. The goal of REBOA is to provide proximal control of abdominal vascular hemorrhage prior to transport to the operating room or angiography suite (Fig. 19-8). After the groin has been prepped, the common femoral artery is accessed with a standard hollow 18-gauge vascular access needle. It is important that incorrect placement, either too proximally into the iliac artery or too distally into the superficial femoral artery, be avoided. As many of these patients may not have a readily palpable femoral pulse, the artery can be accessed using standard anatomical landmarks, ultrasound guidance, or via direct exposure through an open cutdown. Once the artery is accessed, a 0.035-inch wire is fed through the needle in standard Seldinger fashion. Traditionally, a 6 Fr vascular sheath and dilator are placed and then upsized to an 11 to 14 Fr sheath depending on the size of the balloon being used; however, newer “one-pass” sheaths and dilators are currently in production for the trauma setting. Once the appropriate size sheath is in place, a stiff Amplatz guidewire is placed through the sheath. The balloon device is then fed over the guidewire to the correct position.
The location of the balloon in the aorta is determined by the presumed location of the trauma, divided into three distinct zones (Fig. 19-9). Zone I is the proximal zone of the descending aorta between the left subclavian and celiac trunk. Placement of the balloon in this zone is recommended for
abdominal and visceral trauma. Zone II encompasses the abdominal vasculature from the celiac artery to the lowest renal artery. Placement of the balloon in Zone II is contraindicated, as it is possible to directly occlude the celiac artery, superior mesenteric artery, or renal arteries, resulting in organ ischemia. Zone III extends from the lowest renal artery to the aortic bifurcation. Positioning of the balloon in this zone provides proximal control for pelvic hemorrhage while still maintaining perfusion to the abdominal organs. Correct positioning of the balloon can be accomplished with either fluoroscopy, plain film radiograph in the trauma bay, or by physical landmarks.\textsuperscript{135}
FIGURE 19-9  Aortic zones for positioning of REBOA device. Zone I between subclavian artery and celiac artery, Zone II between the celiac artery and the lowest renal artery, and Zone III between the lowest renal artery and the aortic bifurcation.

Once positioned, the balloon is then inflated with either saline or a 1:1
mixture of saline and contrast if fluoroscopy is being utilized. Appropriate filling of the balloon can be confirmed by either visualization of the balloon flattening against the wall of the aorta if using fluoroscopy, or loss of a pulse in the contralateral femoral artery. Several animal studies have demonstrated that aortic occlusion times greater than 60 minutes may result in severe physiological derangement and irreversible organ failure, thus it is imperative that the surgeon be mindful of the duration of balloon inflation and should limit this to less than 60 minutes. After hemorrhage has been controlled, the balloon should be slowly deflated with ongoing communication between the surgeon and the anesthesiologist, as there may be abrupt periods of hypotension as the balloon is deflated. Prior to sheath removal, the common femoral artery should be exposed and the arteriotomy should be closed transversely with 5-0 or 6-0 monofilament suture.

Concerns regarding the use of REBOA focus on incorrect placement of the device, effectiveness in controlling hemorrhage, and potential for organ ischemia. One of the initial case series in 1989 documented the use of REBOA in trauma patients and found that trauma surgeons were able to appropriately position and deploy the balloon and the balloon was able to control hemorrhage in 11 out of 21 patients with refractory hemorrhagic shock.136 Brenner and colleagues published a recent case series of six trauma patients with severe hemorrhagic shock in which REBOA was utilized prior to angiographic or surgical control of the hemorrhage. REBOA resulted in an average increase in systolic blood pressure of 55 mm Hg, and none of the patients died as a result of hemorrhage.137 Additional studies have shown similar rates of successful placement and control of hemorrhage in patients with both blunt and penetrating abdominal trauma.138,139

While in many situations the most effective method to control hemorrhage will be direct control via laparotomy or embolization, REBOA is a technically feasible and potentially life-saving adjunct in the patient with refractory and end-stage hemorrhagic shock. As the technology for the REBOA devices improves and more clinical research is performed, REBOA will likely become more widespread as a rapid and effective method of hemorrhage control prior to definitive surgical repair for life-threatening abdominal and pelvic trauma.

CONCLUSION
In addition to the management of abdominal trauma that has been described throughout the chapter for both blunt and penetrating trauma, there are several proposed treatment paradigms for many of the injuries sustained in trauma. However, the standard-of-care management for an individual is heavily dependent on the resources and personnel available, along with transport options, if any. Resource-rich trauma systems exist throughout the country, with highly qualified personnel. However, these systems are not uniform throughout the nation and the concept of regionalization has not been perfected for all regions. The overarching goal remains the same: optimal management for everyone, regardless of where the patient receives trauma care.

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ABDOMINAL VASCULAR EMERGENCIES
John J. Ricotta • Cameron M. Akbari

INTRODUCTION

Among the many acute abdominal conditions that confront the general surgeon, disorders involving the vascular system are in the minority. Yet these conditions are often highly lethal if undiagnosed or inappropriately treated. Because operations involving vascular exposure, control, and repair are uncommon in the practice of most abdominal surgeons, a straightforward plan to identify and manage these conditions is required for optimal success. This chapter concerns itself with the general diagnosis of acute vascular abdominal conditions, principles of vascular control and repair, and a discussion of the management of the 3 most common types of vascular emergency: mesenteric ischemia, ruptured abdominal aneurysm, and abdominal vascular trauma. Whenever possible, emphasis is placed on general principles that can be applied to a variety of conditions. Acute pathology of the gastrointestinal tract that results in hemorrhage (eg, bleeding ulcer, esophageal varices, bleeding diverticula) is not considered within this chapter.
GENERAL DIAGNOSTIC CONSIDERATIONS

Acute vascular conditions can be divided into those associated with hemorrhage and those accompanied by vascular thrombosis. The presentation within each of these 2 broad categories is generally distinct. Conditions associated with hemorrhage present with evidence of blood loss including shock. Hemodynamic alterations, for example hypotension and tachycardia, predominate over physical findings. Signs of an “acute abdomen,” specifically peritoneal irritation, are often absent. While abdominal pain is usually present, it is often focal and may be associated with a palpable abdominal mass. Signs of shock in the absence of generalized peritonitis or visceral perforation should prompt the consideration of a vascular emergency. In contrast, vascular thrombosis leads to intestinal ischemia and perforation. The clinical presentation of vascular thrombosis is often identical to that of other acute nonvascular abdominal conditions that cause an acute abdomen. Stigmata of cardiovascular disease, for example peripheral vascular occlusions, history of cardiac disease, atrial fibrillation, vascular bruits, and advanced age, should all increase the clinical suspicion of a vascular event as the underlying cause of symptoms. Nevertheless, thrombotic vascular complications often remain undiagnosed until the time of laparotomy.

While physical examination may help to identify patients with intra-abdominal or retroperitoneal bleeding (signs of hemorrhagic shock, absence of peritonitis), routine laboratory evaluations are less helpful. Acute hemorrhage may not result in changes in hemoglobin in its early stages. Laboratory studies are generally useful in excluding other acute inflammatory states, such as pancreatitis, and acute processes of the biliary tree or intestine. Plain films of the abdomen may reveal vascular calcifications or suggest hemorrhage (loss of psoas shadow) but are often nondiagnostic. Computed tomography (CT) scanning, when available, is the most useful preoperative diagnostic study (Fig. 20-1). With the addition of intravenous contrast, CT angiography (CTA) can identify vascular calcifications, aneurysms, and pseudoaneurysms; localize and quantify blood loss; and often identify thrombosis of major arterial and venous structures. Refinements in CTA, such as 3-dimensional (3D) reconstructions, have markedly reduced the need for diagnostic angiography and streamlined the evaluation of all patients with acute abdominal problems. In addition to visualizing vascular structures, nonvascular findings on CT scan may raise the suspicion of an acute vascular
Thickening of the bowel wall and pneumatosis intestinalis may be present without an identifiable lesion in the mesenteric arterial or venous system. Evidence of visceral embolization, particularly in the spleen or liver, should suggest a proximal embolic source, most often from endocarditis. Evidence of a shrunken kidney is a sign of visceral atherosclerosis and, while a nonspecific finding, should increase suspicion of disease in other visceral beds.

**FIGURE 20-1** Noncontrast CT scan demonstrating calcium in the wall of the aorta (*dark arrow*) and retroperitoneal hematoma with fresh blood (*white arrow*) diagnostic of ruptured abdominal aortic aneurysm (AAA).

CT scanning cannot identify all acute vascular conditions, particularly when intravenous contrast is not administered, and scans may not be performed before laparotomy in a number of emergent cases. Under these circumstances, the diagnosis of an acute vascular emergency is made at the time of laparotomy. Most often this diagnosis is obvious on clinical grounds, identification of a mesenteric or retroperitoneal hematoma, presence of free...
blood in the abdomen, or the presence of infarcted bowel without evidence of internal hernia.

**VASCULAR EXPOSURE AND CONTROL**

Expeditious vascular exposure and control is essential for optimal management of vascular emergencies. The principles of operative vascular control are well established: proximal and distal control in a relatively normal area of the vessel. Proximal control should always be established before the lesion is addressed. When attempts to establish distal control would result in excessive dissection or cause damage to adjacent tissues and organs, the vessel is opened after proximal control is established and distal control established intraluminally by placing balloon catheters to control back bleeding. Increasingly, intraluminal techniques are being used for establishing proximal arterial control from remote access sites. Antegrade intravascular balloon control can be established without concern for balloon migration from arterial pulsation. A good example of this is placement of an arterial occlusion balloon in the suprarenal abdominal aorta through the arm vessels. When the balloon catheter is placed from a site distal to the artery (retrograde control), the balloon must be buttressed to avoid migration as a result of the repetitive force of arterial pressure. This can be done by supporting the catheter and balloon by a rigid sheath on which the balloon can rest. Balloon catheters can be used to tamponade proximal collateral bleeding if the main arterial inflow has otherwise been controlled. The most common example of this is the combination of supraceliac clamping coupled with placement of a Foley catheter to control collateral visceral back bleeding during repair of a ruptured aortic aneurysm.

In cases of active hemorrhage or when dissection is difficult, initial venous control is usually obtained by external pressure. Extensive venous dissection is usually avoided to reduce iatrogenic venous damage. Circumferential venous dissection must be meticulous because of the many venous tributaries and the fragility of the vein wall. Intraluminal balloons can be combined with external compression for both proximal and distal control in cases of venous injury, because this is a low-pressure system and catheter dislodgement is not a problem.

Endovascular techniques have been applied across all aspects of vascular
surgery, and management of abdominal vascular emergencies is no exception. However, the application of most of these techniques requires angiographic capabilities in the operating room and significant endovascular experience. In routine practice, the most expeditious way to achieve control remains open exposure. Endovascular techniques remain most useful when they replace extensive or dangerous open dissection. While endovascular options will be discussed within the context of each disease process, these approaches will not be described in detail within this chapter. What follows is a description of the open surgical approach to control of the major abdominal vessels.

**Exposure of the Aorta**

**SUPRACELIAC EXPOSURE**

Expeditious supraceliac control of the abdominal aorta is the most important and versatile technique in the management of abdominal vascular emergencies. While suprarenal, intrarenal, and occasionally supramesenteric controls of the aorta are all possible, there is no evidence that these prove superior to supraceliac aortic control as long as visceral ischemia is limited to 45 minutes or less. Supraceliac aortic control can be achieved rapidly with very little risk of damage to adjacent organs such as the intestines, pancreas, or vena cava or the visceral vessels. Finally, the supraceliac aorta is most likely to be free of either aneurysmal or atherosclerotic vascular disease. For this reason, exposure and control of the aorta at that level is easier and safer than control between the visceral vessels. Supraceliac control of the aorta through a left retroperitoneal approach has been well described but is not germane in this situation, because it precludes evaluation of the abdominal viscera. Therefore, only the transabdominal exposure of the supraceliac aorta is described.

The supraceliac aorta is approached through the gastrohepatic ligament, which is divided between clamps (Fig. 20-2A). The left lobe of the liver is mobilized by dividing its diaphragmatic attachments if necessary. Division of the gastrohepatic ligament brings one directly down on to the esophagus and aorta as they course through the diaphragmatic hiatus. The aorta lies to the right of the esophagus and should be easily palpable. In the event that the 2 organs are not easily distinguishable, a nasogastric or orogastric tube may be
placed in the esophagus to aid in distinguishing, but this is rarely required in our experience. Once the aorta has been identified, the key to obtaining control is complete division of the fibers of the left crus of the diaphragm as they cross the anterior aspect of the aorta (Fig. 20-2B). This can be done by placing either the index finger or a large-angled clamp between the aorta and the crural fibers as they cross over its anterior aspect. The fibers are divided, slightly to the left of the midline (“2 o’clock” position) to avoid bleeding, either with scissors or electrocautery. The phrenic arteries are identified and either clipped or, preferentially, spared. One cannot overemphasize the importance of completely dividing these fibers and clearing the anterior, medial, and lateral aspects of the aorta prior to applying the vascular clamp. If this is not done, any aortic clamp will slip anteriorly, resulting in loss of aortic control with disastrous results. Once the crura are divided, the aorta is encircled between the thumb and index finger of the operating surgeon’s right hand (Fig. 20-2C). The aorta is then lifted gently off the spine to be sure that it has been completely mobilized. A clamp can then be reliably placed across the aorta. More extensive dissection of the aorta is not required, and we avoid passing angled clamps and loops under the aorta to minimize damage to intercostal vessels. Use of the index finger and a straight aortic clamp are all that is required.
**FIGURE 20-2** Exposure of suprarenal aorta. **A.** Division of gastrohepatic ligament. **B.** Line of incision in left crus of diaphragm to expose aorta. This is facilitated by placing a finger or a clamp between aorta and crural fibers. **C.** The aorta is then encircled bluntly using finger dissection.

**EXPOSURE OF THE VISCERAL AORTA**

This area of the aorta will rarely need to be exposed for acute vascular emergencies. Transperitoneal control of the visceral aorta requires a left medial visceral rotation.\(^7\) The left colon is mobilized along Toldt’s line (Fig. 20-3A), the retroperitoneal and phrenic attachments of the spleen are divided,
and the spleen, colon, and tail of the pancreas are reflected medially, leaving the left kidney down (Fig. 20-3B). This results in exposure of the anterior aspect of the aorta, and the origins of the renal, celiac, and superior mesenteric arteries (SMAs). If exposure of the posterior aspect of the aorta is required, the left kidney is elevated with the other viscera (Fig. 20-3C). Exposure of the visceral vessels more distally is described as follows.
FIGURE 20-3  Left medial visceral rotation. A. Mobilization of the left
colon along Toldt’s line. The spleen and pancreas are also mobilized. B. With reflection of the spleen, pancreas, and colon anteriorly toward the midline, the anterior aspect of the aorta is exposed along with the origins of the left renal, superior mesenteric, and celiac arteries. The aortic hiatus of the diaphragm may need to be incised to provide additional cephalad exposure. C. If access to the posterior aspect of the aorta is required, the left kidney is mobilized outside Gerota’s fascia, along with the other viscera.

INFRARENAL AORTIC EXPOSURE

This technique is familiar to most surgeons and involves incision of the ligament of Treitz and mobilization of the fourth portion of the duodenum superiorly and to the right (Fig. 20-4). When encountered, the inferior mesenteric vein may be divided between clamps. This sometimes improves exposure and is preferable to leaving an intact vein under tension with the risk of avulsion. The left renal vein serves as a reference to identify the superior extent of dissection. This vein almost never requires division. Should additional mobilization be required, the gonadal and lumbar veins can be divided for superior mobility and the adrenal vein is divided if the vein is to be retracted inferiorly. If these collaterals are divided and the renal vein is subsequently sacrificed, it should be repaired, either primarily or with an interposition graft. If the left renal vein is not encountered during this dissection, one must consider the possibility of an aberrant renal vein coursing posterior to the aorta, which occurs in 1% of patients. In that case, the vein is at risk for damage during aortic cross clamping and particular care should be taken during the posterior dissection of the aorta.
A 30-degree 5-mm scope is inserted and initial inspection commenced with attention to the presence of ascites, omental/peritoneal nodules, or liver masses. Next, additional trocars are placed in a manner that allows the region of primary interest to be examined with a head-on view and instrument ports to be aligned with the viewing angle (Fig. 7-1). The number and size of additional trocars will depend on the need for biopsies and other interventions, though a complete diagnostic laparoscopy with cup biopsies of the liver or peritoneum will generally require two additional 5-mm trocars. If peritoneal cytology is to be performed, it is done prior to manipulation or dissection of tissues by instilling 250 mL normal saline into each of the upper
quadrants and aspiration into a Lugol’s trap.

Lymphatic and areolar tissue anterior to the aorta is cauterized or divided and ligated between clamps. It is better to ligate large lymphatics to prevent chyle leak postoperatively. As with the suprarenal aorta, the vessel is encircled using the thumb and index finger and lumbar vessels usually do not require division. We are more inclined to place a tape around the aorta in the infrarenal location, because visualization is optimal, but this is not required. As described previously, the aorta is circumferentially mobilized digitally, raised off the spine, and an aortic cross clamp is placed under direct vision (Fig. 20-5).
FIGURE 20-5 Control of the aorta by finger dissection. The aortic neck can be elevated off the spine and a clamp applied.

**Exposure of the Iliac Arteries**

The common and external iliac arteries are controlled after entering the retroperitoneum. For proximal iliac control, the small bowel mesentery is reflected to the right and the aortic bifurcation is exposed. For more distal control, particularly of the external iliac arteries, the right or left colon is
mobilized along Toldt’s line and reflected toward the midline (Fig. 20-6). It is important to be mindful of the ureter as it crosses over the iliac bifurcation. Control of the iliac arteries at the aortic bifurcation can be dangerous because of the confluence of the iliac veins behind the right iliac artery. This is one of the most common sites of iatrogenic vascular injury during aortoiliac surgery. The venous structures are gently separated from the arteries by use of blunt dissection (sponge on stick, kitner dissector, or digital dissection). We avoid use of clamps to dissect around the iliac vessels whenever possible. Once the vessels are separated from the adjacent venous structures, they can be encircled with vessel loops and clamped. Relatively blind clamping of the iliac arteries without dissection away from surrounding veins is discouraged as venous injury may result with disastrous consequences.
FIGURE 20-6 Exposure of the distal iliac vessels is performed by incising the lateral attachments of the sigmoid or cecum and retracting the bowel medially. Note the ureter as it crosses the iliac bifurcation.

The hypogastric arteries and distal external iliac arteries can be difficult to expose, particularly in a deep pelvis. The hypogastric artery in particular may present challenges with the risk of injury to deep pelvic veins. This artery can usually be controlled by retrograde balloon tamponade and oversewn. The very distal external iliac artery can be controlled with an intravascular balloon and, if necessary, oversewn. Vascular continuity can be restored by a bypass to the common femoral artery.
EXPOSURE OF THE CELIAC ARTERY AND ITS BRANCHES

Exposure of the proximal celiac artery can be obtained through the gastrohepatic ligament, as described for the suprarenal aorta, or by left medial visceral rotation. We prefer the former approach whenever possible. The celiac artery is identified as it originates from the aorta at the diaphragmatic hiatus. Division of diaphragmatic fibers facilitates proximal exposure. More distal control is achieved by careful dissection along the anterior aspect of the vessel with caudal traction on the stomach and superior border of the pancreas. The tissue surrounding the vessel is carefully divided and ligated.

By opening the gastrohepatic ligament along the lesser curvature of the stomach, one can trace and isolate the common hepatic artery superior to the pancreas. The proper hepatic artery courses in the portal triad anterior and medial to the portal vein. The standard techniques for exposure of the porta hepatis will serve to identify and isolate this structure. The splenic artery is exposed by entering the lesser sac and reflecting the pancreas inferiorly and anteriorly. The multiple branches of this vessel that supply the pancreas must be ligated for adequate exposure. The distal splenic artery is best exposed by mobilizing the spleen as for splenectomy.

EXPOSURE OF THE SUPERIOR MESENTERIC ARTERY

Transabdominal control of the superior mesenteric artery (SMA) at its origin requires medial visceral rotation of the left colon, spleen, and tail of the pancreas. Exposure of the more distal SMA can be done through the base of the small bowel mesentery or by approaching the vessel on its posteromedial aspect after reflecting the small bowel mesentery to the right (as in standard aortic exposure). In the former approach, the transverse colon is elevated and the middle colic vessel is traced down to the SMA in the small bowel mesentery (Fig. 20-7). The anterior aspect of the vessel is cleared, taking care not to injure the adjacent vein. In the latter approach, the vessel is palpated in the root of the small bowel mesentery and dissection proceeds on the lateral aspect of the vessel (see Fig. 20-4A). In either case, dissection requires meticulous division and ligature of small venous, arterial and lymphatic branches, and the preservation of as many major arterial and venous branches as possible.
FIGURE 20-7 Exposure of the superior mesenteric artery (SMA) through the mesocolon. The colon is lifted cephalad and the small bowel mesentery pulled caudally. The middle colic artery is identified and followed down to the SMA. Alternative SMA exposure is shown in Fig. 20-4A.

EXPOSURE OF THE RENAL ARTERIES
Transperitoneal control of the renal arteries can be achieved in a variety of ways, depending on the area of the artery to be controlled. The left renal artery is exposed in the same manner as the infrarenal aorta. The artery is usually superior and posterior to the left renal vein. The renal vein may require mobilization, including division of its lumbar, gonadal, or adrenal tributaries. Occasionally, the retroperitoneal attachments at the inferior border of the pancreas must be incised so the pancreas can be retracted in a cephalad fashion. The renal artery can be traced distally from its origin at the aorta. If the distal renal artery, near the hilum of the kidney, requires exposure, this is most easily done by mobilizing the left colon toward the midline. This may require mobilization of the splenic flexure and occasionally the tail of the pancreas, although this is not always the case. The proximal right renal artery can be exposed for a short segment between the aorta and inferior vena cava (IVC). The first part of the exposure is similar to that for the infrarenal aorta. Because the right renal artery runs behind the IVC, significant proximal exposure of this vessel requires mobilization of the vena cava and retracting it to the right. This requires careful division of 1 and often 2 sets of lumbar veins. Even with this maneuver, only the most proximal portion of the renal artery is exposed. As a result, the right renal artery is most often exposed by an extended Kocher maneuver; which reflects the duodenum, ascending colon and hepatic flexure toward the midline. The artery again lies posterior and inferior to the renal vein, which often requires mobilization.

EXPOSURE OF THE VENOUS STRUCTURES

The visceral veins are exposed by the same approaches as their corresponding arteries. Exposure of the vena cava and iliac veins requires some discussion. In general, these vessels are not involved in acute abdominal vascular emergencies outside the trauma setting. However, the vena cava is the vascular structure most commonly involved in penetrating abdominal trauma. The IVC and confluence of the iliac veins are generally exposed by a right medial visceral rotation (Fig. 20-8). This involves mobilization of the right colon along with an extended Kocher maneuver rotating the duodenum and head of the pancreas when more proximal venous exposure is required. When exposing venous structures, one must be exceedingly cautious of the fragility of the vessel and, in particular, disrupting small, posterior, lumbar vessels. As a consequence and because the venous system is a “low-pressure”
system, compression plays a greater role in control of the vena cava and iliac veins than it does in exposure and control of the corresponding arterial segments. Circumferential mobilization of the veins is avoided if possible, as is the application of clamps. The use of blunt instruments such as sponge sticks can usually provide adequate hemostasis (Fig. 20-9). Fine clamps, such as Allis clamps, can be used to coapt cut ends of vessels and facilitate either suture or control by applying partial occlusion clamps. Whenever possible, only the anterior segments of the vein are exposed to avoid dissection around the lumbar vessels. Exposure of isolated posterior injuries involves significant mobilization and rotation of the vena cava and often requires ligation of multiple tributaries. Ligation is liberally applied in cases of extensive venous injury.
FIGURE 20-8 Right medial visceral rotation. The right colon, duodenum, and head of the pancreas are mobilized to expose the vena cava, the iliac veins, and the right renal artery and vein. The renal artery is exposed by retracting the vein either cephalad or caudad.
FIGURE 20-9 Control of vena cava. Pressure using digital compression or sponge sticks should be sufficient to control most venous injuries and avoids circumferential dissection.

**PRINCIPLES OF ARTERIAL REPAIR**

Several factors dictate the approach to emergency arterial repair, including the extent of contamination, size of the arterial defect, and the adequacy of collateral circulation. The following are principles that should guide the choice of procedure:

1. When possible, primary repair is indicated. While most circumstances do
not lend themselves to this approach, lateral repair or primary end-to-end anastomosis, or even arterial reimplantation, is associated with good long-term results and avoids use of a conduit.

2. When adequate collateral circulation exists, ligation without repair is an appropriate option. This is the case with most splenic artery aneurysms and selected aneurysms of the hepatic and superior mesenteric arteries.

3. In the absence of contamination, prosthetic conduits provide the best choice for bypass of major intra-abdominal arteries. The high flow in the aorta and major visceral arteries along with their relatively large diameters is associated with good long-term patency of prosthetic bypass. Prosthetic conduits have the advantage of adequate diameter and ready availability, which makes them preferable to saphenous vein in the absence of any contraindication. Occasionally when reconstruction of a small to medium diameter (<6 mm) vessel is required, saphenous vein may be the preferred conduit.

4. In the presence of anything in excess of minor contamination, autogenous material should be used when vascular reconstruction is required. The risk of prosthetic graft infection with rupture argues against its routine use. For small- to medium-sized vessels (<6 mm), or when a patch closure is feasible, saphenous vein is usually adequate. For larger vessels, deep veins (femoral, popliteal, or jugular) should be considered. Short segment arterial repairs (eg, visceral and renal vessels) can be performed with hypogastric artery. Aortoiliac repair in the face of contamination should be performed with either deep leg veins, or more often arterial ligation and extra-anatomic bypass to restore perfusion. In the patient in extremis in whom obtaining autogenous conduit expeditiously is not an option, antibiotic-soaked prosthetic material can be used to salvage the situation, accepting an increased risk of infection and secondary surgery.

**MANAGEMENT OF VASCULAR EMERGENCIES**

**Acute Mesenteric Insufficiency**

**PRESENTATION**
Patients with acute mesenteric insufficiency generally present with abdominal pain out of proportion to their physical findings. However, if undiagnosed, acute ischemia will progress to intestinal infarction with the attendant signs of peritonitis. Laboratory investigations include complete blood count, electrolytes, lactic acid, liver panel, amylase, and lipase. In general, findings are nonspecific early in the course of the disease and consist of a leukocytosis and perhaps some evidence of hemoconcentration. Liver panel, amylase, and lipase are most useful to exclude other acute abdominal conditions. Elevated lactic acid is usually a late sign and associated with a poor prognosis. Plain radiographs are nonspecific. An ileus may be present and occasionally edema of the bowel wall (“thumb printing”) may be present. CT, with intravenous contrast, has emerged as the most useful imaging modality. CT scans can identify abrupt arterial cutoffs, particularly when 3D reconstructions are available. In addition, late-phase CT angiography is the most reliable means to identify mesenteric vein thrombosis. Occasionally, angiography may be required, particularly when nonocclusive mesenteric ischemia (NOMI) is suspected. In these cases, angiography may be both diagnostic and therapeutic.

Mesenteric ischemia results from a variety of conditions; the most common is arterial thrombosis, followed by arterial embolism, low-flow states, and mesenteric venous thrombosis.\textsuperscript{11–15} Mortality is highest in low-flow (nonocclusive) ischemia and lowest in mesenteric venous thrombosis. Mortality of ischemia resulting from acute arterial occlusion remains 30% to 40%. Diagnosis is delayed in up to two-thirds of patients with mesenteric ischemia. Outcomes in acute mesenteric ischemia are related to the time to diagnosis,\textsuperscript{11,15} and therefore effective treatment relies on prompt diagnosis and initiation of therapy before extensive bowel infarction occurs. This is dependent on a high index of suspicion. Prompt effective fluid resuscitation is important in all cases of mesenteric ischemia, along with the initiation of broad-spectrum antibiotics. Patients with signs of an acute abdomen should be taken to the operating room as soon as they have been adequately resuscitated. Beyond this, however, the specific management of each type of mesenteric ischemia differs somewhat according to the etiology. Therefore, they are discussed separately.

\textit{Acute mesenteric embolization} presents with the sudden onset of severe abdominal pain in the setting of a relatively normal abdominal examination. Most emboli are of cardiac origin and the patient may have an irregular pulse,
cardiac murmur, or a history of prior myocardial infarction. Many patients may have a history of atrial fibrillation and/or prior embolic events. Because of the flow characteristics of the visceral vessels, most emboli preferentially go to the SMA. While some emboli lodge at the origin of this vessel, most end up distal to the first jejunal branches. An abrupt cutoff of flow in the SMA distal to the first jejunal branches on catheter angiography or CT angiogram is diagnostic of this condition (Figs 20-10 and 20-11). Treatment is generally laparotomy and embolectomy. Characteristically, the most proximal jejunum is viable in the case of SMA embolus, because the occlusion occurs distal to the first jejunal branches. This is a helpful, but not foolproof, way to differentiate mesenteric embolization from mesenteric thrombosis.

**FIGURE 20-10** Angiogram of superior mesenteric artery (SMA) embolus demonstrating an abrupt cutoff distal to a branch point. Note the replaced right hepatic artery (white arrow), a common vascular anomaly.
As described earlier in this chapter, the SMA is exposed. The artery is usually soft and the site of the embolus is readily apparent. While a transverse arteriotomy with primary repair can be done, we prefer a longitudinal arteriotomy, and patch closure in most circumstances. The longitudinal arteriotomy can be extended if necessary and will allow thorough examination of the vessel and meticulous closure. It also facilitates bypass should this be required. Once the artery is opened, 3-F and 4-Fr embolectomy catheters are passed both proximally and distally to reestablish flow. If necessary, papaverine, 1 mg/kg, or 100 μg of nitroglycerine can be instilled in the distal vessels to reduce vasospasm. When there is concern about residual distal thrombus, 250 mg of urokinase or 1 to 3 mg of tissue plasminogen activator (TPA) in 50 mL saline can be instilled in the distal vascular bed.\textsuperscript{16} If there is clinical evidence of atherosclerosis in the artery, a longitudinal arteriotomy and patch closure are mandatory. If bowel resection is required, proximal saphenous vein should be used for arterial reconstruction.

In unusual circumstances, catheter-directed thrombolysis can be used as an alternative to open embolectomy.\textsuperscript{17} The patient should have no signs of peritonitis and angiography should demonstrate distal emboli (not easily retrieved by an embolectomy catheter) or a partially occluding proximal embolus that permits distal flow to continue during thrombolysis. In these
rare circumstances, an infusion of TPA directly into the SMA can be attempted. Mechanical thrombolysis should not be attempted because of the danger of distal embolization. The patient must be observed carefully during lysis for signs of deterioration and any concern over bowel viability will prompt laparotomy. Best results are seen when symptoms show some resolution within 1 hour.¹⁸

The clinical signs of *acute mesenteric thrombosis* are indistinguishable from those of acute embolic occlusion; however, there are often differences in the history and some physical findings. History of arterial occlusive disease (stroke, claudication, myocardial infarction) is common, and atrial fibrillation or prior embolic episodes are less frequent. Careful questioning may elicit a history of chronic postprandial pain and weight loss, characteristics of chronic mesenteric ischemia. Physical examination often reveals stigmata of atherosclerosis, for example absent pulses and vascular bruits. Angiographic findings usually reveal diffuse atherosclerosis of the aorta and visceral vessels with multivessel involvement. When vascular occlusion occurs, it is usually at the origin of the mesenteric vessels (Fig. 20-12).¹⁴
FIGURE 20-12 CT scan of superior mesenteric artery (SMA) thrombosis at the origin of the vessel. This is usually due to underlying atherosclerosis. Emboli lodge at the origin of the SMA in about 30% or fewer of cases.

The operative approach to acute thrombotic mesenteric ischemia differs from that of embolic occlusion. Mesenteric flow cannot be restored by a simple embolectomy and alternatives are required. The most common procedure required is bypass of the SMA usually from the infrarenal aorta or from one of the iliac arteries. While suprarenal bypass is preferred in elective surgery for chronic ischemia, an infrarenal origin of the bypass is more expeditious in the acutely ischemic patient and avoids the acute hemodynamic consequences of suprarenal clamping in a patient already acutely ill and often hemodynamically compromised. Because bowel resection is usually required, autogenous saphenous vein is the preferred conduit and should be harvested from the proximal thigh. When the bypass is performed, there should be sufficient redundancy to allow a “lazy C” loop, traveling from right to left in the abdomen to avoid sharp kinking (Fig. 20-13). The bypass is usually performed on the lateral side of the SMA slightly
posterior, so that it can lie without compromise when the viscera are returned to the abdomen. While it is tempting to use very short bypasses, these may be prone to kinking and perioperative thrombosis. In the acute setting, revascularization is usually restricted to the SMA alone.

**FIGURE 20-13** Retrograde bypass of superior mesenteric artery (SMA) occlusion. This can originate from the aorta or the right iliac artery. The “lazy
C” loop reduces the chance of graft kinking. The SMA anastomosis is on the posterolateral aspect of the vessel. While a prosthetic graft is pictured here, the saphenous vein should be used when contamination is a concern.

When there is no suggestion of intestinal necrosis and angiography reveals high-grade stenosis rather than vascular occlusion, an endovascular approach may be attempted.\textsuperscript{19,20} Although an endovascular approach has been favored by many in patients with chronic mesenteric ischemia, it is more problematic in the acute setting. Endovascular recanalization is more dangerous when vessels are completely occluded because of the possibility of causing distal embolization. While the target lesion remains the SMA, it is reasonable to perform angioplasty of multiple visceral arteries if the patient remains stable. The visceral vessels may be engaged either transfemorally or more often via a transbrachial approach. The latter facilitates access to the origin of the vessel and passage of angioplasty balloons and stents as required. If there is any indication of intravascular thrombus, lytic infusion should be performed prior to any attempt at angioplasty to avoid the possibility of distal embolization. Once the possibility of thrombus is excluded, angioplasty with the placement of a balloon expandable nitinol stent is then performed. Use of a short (15-20 mm) 5- to 6-mm–diameter balloon–expandable stent allows precise deployment. The stent should completely traverse the area of narrowing and extend a few mms out into the aorta. This is important because the lesion in this case usually has its origin in the aorta. Selecting an endovascular approach does not mean that laparotomy is avoided, because bowel ischemia may be present. Any signs of peritonitis require prompt laparotomy and inspection of the bowel for viability.

Retrograde endovascular recanalization of a proximal SMA lesion has been reported at the time of celiotomy.\textsuperscript{21} This technique involves a longitudinal arteriotomy made in the SMA and passing a wire retrograde into the aorta under fluoroscopic guidance. Balloon angioplasty of the proximal lesion is performed as an alternative to bypass, and the arteriotomy is closed with a patch. While reports are anecdotal, this procedure is of interest because it avoids the possibility of distal embolization and may be performed more expeditiously than a vein bypass.

Nonocclusive mesenteric ischemia (NOMI) may occur as the result of low flow, without evidence of acute arterial thrombosis or embolization. In one form of this condition, the colon, in whole or in part, is involved. The arterial
supply of the colon is less robust than that of the small bowel and, in elderly patients particularly, the inferior mesenteric artery (IMA) may be diseased or occluded. Systemic illness with reduced visceral blood flow, or abrupt interruption of the IMA, such as with aortic resection, may precipitate infarction of marginally perfused areas of the colon. This is most common in the sigmoid colon and the splenic flexure. The rectum is often spared in this process, because of its dual supply through the hemorrhoidal vessels. The small bowel is also usually spared. In these situations, resection of the infarcted colon, with exteriorization and diversion as necessary, is all that is required. The SMA and celiac arteries are usually normal, and no attempt at revascularization of the IMA is indicated.

Mesenteric ischemia without an underlying visceral lesion may also involve the SMA and celiac distribution. This has been called “nonocclusive mesenteric ischemia” (NOMI) and is associated with severe systemic illness, hypotension, and spasm of the mesenteric vessels without evidence of an obstructive lesion. Patients with NOMI are often already in an intensive care unit (ICU) and have had a cardiac event requiring vasoactive drug infusions. Some patients may have been on digitalis preparations that themselves are known to reduce visceral blood flow. There have been some recent reports of NOMI following dialysis in patients with end-stage renal disease. Angiography, when performed, shows “pruning” of the mesenteric vessels without discrete obstruction. Management of these patients is directed at overall cardiovascular support, treatment of the underlying acute condition(s), and broad-spectrum antibiotics. Intra-arterial papaverine may be administered to relieve vascular spasm, although this is not always effective and may be complicated by systemic hypotension. NOMI usually portends a bad outcome in general, which is related as much to the underlying illness as to mesenteric compromise. Laparotomy should be reserved for patients in whom intestinal infarction is suspected and who are deemed otherwise salvageable since it often will not influence the outcome in this disease.

Mesenteric venous thrombosis may result in acute intestinal ischemia, although this accounts for only about 5% of all cases. Patients are a distinct subgroup, being younger (30-50 years) and predominantly female. Associated hypercoagulable state can be identified in more than three-quarters of patients and a history of prior venous thrombosis is not uncommon. Common inherited states include deficiencies of protein C, protein S, and antithrombin III; activated protein C resistance; factor V
Leiden mutation; and methylenetetrahydrofolate mutations. Acquired prothrombotic states include profound dehydration, polycythemia, cancer, pelvic or abdominal inflammation, and hormone use. Mesenteric venous occlusion is most readily diagnosed by venous-phase CT angiography, which can demonstrate thrombus in the superior mesenteric vein and portal system (Fig. 20-14). Early diagnosis, and therefore a high clinical index of suspicion, and prompt initiation of systemic anticoagulation are critical to success. Operative findings suggestive of this condition are edematous beefy red bowel with thrombus in veins of the mesentery. The primary mode of therapy is anticoagulation; operative intervention is reserved for situations when bowel necrosis is suspected and resection is required. In those situations, limiting resection with a “second-look” laparotomy, along with ongoing anticoagulation, is the appropriate course. Most patients can be managed supportively, although significant volume resuscitation may be required. There are anecdotal reports of mesenteric and portal vein thrombectomy and thrombolysis, but these do not reflect the standard of care for most patients.

FIGURE 20-14 CT scan demonstrating thrombus in the superior mesenteric
vein. CT scan is the most accurate diagnostic study in this condition.

DETERMINING INTESTINAL VIABILITY: THE ROLE OF “SECOND-LOOK” SURGERY

A major challenge in managing patients with intestinal ischemia is assessing the need for, and extent of, intestinal resection. Preoperatively, colonoscopy can be used to assess the viability of the large intestine in questionable situations. Friable red mucosa suggests viability and a grey mucosa that readily sloughs indicates the need for resection. Viability of the large bowel is difficult to judge from external appearance at the time of laparotomy, and in general, it is preferable to err on the side of resection in questionable circumstances, because maintaining large bowel length is not an absolute requirement for survival. Primary repair should not be undertaken after large bowel resection; diversion with secondary reconstruction is preferred.

When the small intestine is involved, the problem becomes more complex. Every effort should be made to preserve as much small bowel as possible. Clearly necrotic segments of bowel and areas of perforation are excluded immediately to prevent contamination during vascular reconstruction and subsequently resected. Evaluation of the remainder of the small bowel is done after blood flow to the intestine is restored. The bowel is usually observed for 15 to 20 minutes after revascularization and warm lap pads are applied to the intestines to reduce any vasospasm. External inspection, with attention to color and peristalsis, is more helpful than in the large bowel. Doppler interrogation of the antimesenteric border for arterial flow is useful when positive. Use of fluorescein (1 ampule given intravenously) followed by inspection with a Wood’s lamp, is the most sensitive means of determining perfusion. Viable bowel will be fluorescent yellow while nonperfused bowel will appear dark purple. When the extent of resection is minimal and the remaining bowel is clearly viable, anastomosis and abdominal closure is reasonable. When there are large areas of questionable bowel that might mandate extensive resection, an alternative approach is undertaken. Under these conditions, marginal segments of bowel are left in situ and their ends are simply closed over and returned to the abdomen. Plans for a second operation are made. Stomas are not performed at this stage to preserve intestinal length. Fluorescein is not used at this time but reserved for the second procedure. The abdomen is temporarily closed
using a “Bogotá bag,” polytetrafluoroethylene (PTFE) patch, or other temporary appliance (to minimize the chance of abdominal compartment syndrome) and the patient is returned to the ICU where resuscitation continues. A subsequent laparotomy is performed at 18 to 24 hours, after the patient has been stabilized. At this point fluorescein is injected and nonviable bowel is resected. Intestinal continuity is restored unless it is unsafe to do so. The abdomen often cannot be closed primarily at this point because of the danger of compartmental hypertension, and an “open abdomen” approach with delayed closure may be needed. Any deterioration in the patient’s subsequent hospital course should suggest breakdown of an anastomosis and prompt the appropriate therapy.

Despite increased clinical awareness and advances in diagnostic modalities and perioperative care, management of intestinal ischemia remains a significant challenge to the most experienced surgeon with continued high mortality and morbidity.

Management of Abdominal Vascular Trauma

Vascular injuries occur in 10% to 15% of cases of blunt and penetrating trauma.\textsuperscript{34–38} Associated nonvascular injuries are seen in over 90% of patients with vascular trauma, most commonly small bowel, colon, and liver.\textsuperscript{37} Vascular injuries can be highly lethal when they occur and remain the most common cause of death following penetrating abdominal trauma. Arterial and venous injuries occur with equal frequency. The pattern of injury differs between blunt and penetrating injuries. In penetrating injuries, the most commonly injured vessels are the vena cava, followed by the aorta, iliac arteries and veins, and the SMA, and vein and multiple vascular injuries are common.\textsuperscript{10} Vessels of the mesentery are the most commonly involved in blunt trauma. This section provides principles for management of injuries to the major arteries and veins of the abdomen and retroperitoneum. The reader is referred to the prior sections on vascular exposure for a description of how to obtain control of these vessels. The discussion here centers on management of specific injuries.

Overall, principles of trauma management including initial resuscitation of the patient, rapid evaluation and triage, and expeditious operation when indicated should prevail. Stable patients, particularly those with blunt trauma,
may undergo one or more diagnostic tests, including peritoneal lavage, “FAST” ultrasound examination, and, with increasing frequency, CT scan. Many patients with penetrating trauma are taken directly to the operating room without further diagnostic evaluation. Consequently, in a significant proportion of cases, the extent of vascular trauma is not known preoperatively and must be assessed by the surgeon in the operating room. Intraperitoneal hemorrhage is easily recognized and should be expeditiously controlled, by application of external pressure, vascular clamps, or intravascular balloon occlusion catheters. Once active hemorrhage is controlled, any visceral perforation is controlled by exclusion to prevent ongoing peritoneal contamination and any remaining solid-organ injuries (ie, liver, spleen, and pancreas) should be stabilized by packing. Definitive treatment of the vascular injuries should then receive priority over definitive visceral repair. The adaptation of a “damage control” approach to abdominal trauma has improved outcomes in abdominal trauma. Vascular “damage control” involves the control of major venous injuries by ligation or packing and placement of temporary shunts to restore arterial continuity when arterial ligation will not be tolerated. Shunts are most often used to temporarily restore flow to the extremities but are used less often in management of visceral injuries. In general, visceral vessels are either repaired or ligated during the initial operation. The end organ will either tolerate ligation because of collateral circulation or be sacrificed. The “damage control” concept combined with endovascular techniques may be of particular use when open vascular repair is exceedingly complex and associated with significant morality. This is particularly true of contained retroperitoneal or hepatic injuries. Definitive treatment can be deferred at initial laparotomy in these cases and attempted in an imaging suite using endovascular techniques after the patient is stabilized. Examples of this include embolization of intrahepatic arterial injury and treatment of some contained retroperitoneal hematomas. This approach is in evolution and holds significant promise. There are a number of situations in which the surgeon must make a decision about whether to explore a contained hematoma. In these cases, the risk of missing a major vascular injury is balanced against the morbidity of operative exploration. Classic trauma training requires exploration of all contained hematomas that result from penetrating injury. In the case of blunt trauma, central hematomas (zone 1) are explored because of the risk of injury to the aorta or vena cava, while lateral and pelvic hematomas are explored.
only if there is active bleeding or expansion under observation. If exploration occurs, it is important to obtain proximal and, whenever possible distal, arterial control outside the area of hematoma before proceeding. Venous control above and below the area of injury is desirable but may not always be obtainable. Approaches to vascular control, including endovascular techniques in various locations, have already been described. Intravascular occlusion catheters should be readily available for additional control as needed. Only after every attempt to control the arterial and venous ingress and egress to the hematoma has been made should it be entered.

The advent of endovascular techniques may be changing the classic paradigm of managing contained hematoma from either blunt or penetrating cause. The rationale for exploring nonexpanding hematomas of any type was based on the concern for occult vascular or visceral injury. The advent of CT angiography and the existence of sophisticated intravascular imagining in the operating room can facilitate evaluation of nonexpanding hematomas from both penetrating and blunt trauma without the need for operative exposure and its attendant blood loss. Furthermore, endovascular techniques such as covered stents or coil embolization will allow treatment of many vascular injuries from remote access with reduced risk of blood loss. Such treatments are in fact preferred for trauma to branch vessels in the visceral, renal, or pelvic circulations. This potential change in paradigm suggests that the surgeon consider a form of vascular “damage control” in the case of contained hemorrhage, by considering an “endovascular first” approach for diagnosis and treatment of contained hematomas regardless of location. This area is currently evolving, and there is no consensus on the role endovascular techniques should and will eventually play. With these general comments in mind, a discussion of specific vascular injuries and their management follows.

INJURIES TO THE SUPRARENAL AORTA AND VENA CAVA

These injuries as a group are highly lethal and management is difficult. They should be suspected in any patient with a central hematoma from either blunt or penetrating trauma. In the stable patient, CT scan with intravenous contrast can help to identify the area of injury. If CT scan is not possible
preoperatively, a clear plan of exposure and management is crucial before commencing any attempt at repair. Because of the advances made in endovascular techniques, patients should be treated in an operating room that has the capability of intraoperative fluoroscopic imaging and angiography whenever possible. If an injury to the aorta or vena cava is suspected and the patient is not exsanguinating, the surgeon should consider intraoperative angiography through the femoral artery or vein as appropriate to evaluate the location and extent of vascular injury and consider intravascular control. Following this, proximal and distal control should be established. Open exposure of the aorta at the diaphragmatic hiatus or endoluminal balloon control,\textsuperscript{3,4} both described previously, can be performed. Injuries to the vena cava can initially be controlled by balloon tamponade, although this may reduce venous return to the right side of the heart. Open control of the vena cava is described in the following text.

**OPEN REPAIR OF THE SUPRARENAL AORTA**

The visceral aorta is exposed by a left medial visceral rotation described previously. If access to the posterior aspect of the aorta is required, the left kidney should be elevated along with the other viscera; if access to the anterior aorta is needed, the kidney is left in its bed. Direct suture repair is undertaken whenever possible. Direct repair that does not narrow the lumen of the aorta more than 50% or impinge on a visceral vessel is well tolerated. Larger defects may require patch angioplasty using prosthetic material, arterial autograft, or arterial homograft. In the absence of significant contamination, prosthetic material provides a readily available, strong, and durable material for repair. In the presence of gross fecal contamination, biologic materials should be used if possible. Arterial homograft provides the most expeditious alternative both for size and durability, if available. Antibiotic-impregnated prosthetic material may be used, after extensive debridement of the area. In these cases, the repair should be wrapped in omentum and the patient should be placed on long-term, perhaps lifelong, antibiotic treatment. Saphenous vein is inappropriate in this circumstance due to concerns about strength and durability; deep veins of the leg have proven reliable substitutes for in situ aortic reconstruction in infected fields.\textsuperscript{46} If appropriate, the aortic repair can be buttressed by an apron of omentum of some paraspinous muscle, to separate the suture line from any visceral...
vessels. This should be done in the presence of associated visceral injury, particularly injury to the pancreas. Drainage is established as needed. If the damage involves the origins of one or more of the visceral vessels, these are ligated. Revascularization of these vessels can be performed as described in the following text. Damage control of the suprarenal aorta is not possible because of the mesenteric ischemia that would attend any such attempt.

ENDOVASCULAR REPAIR OF THE AORTA

This emerging alternative should be considered in selected circumstances. In a stable patient with a contained injury, placement of a suitable covered stent can be combined with extra-anatomic debranching of 1 or 2 visceral vessels, as has been described for treatment of thoracoabdominal aneurysms. This is most suitable when a single mesenteric vessel is involved, because the bowel will tolerate more prolonged ischemia than the kidney. Modification of the stent graft (“fenestrations”), to allow continued visceral perfusion, is possible. This is most feasible when the aortic defect is posterior and relatively remote from the visceral orifices. More precise fenestrations, as required in suprarenal aortic repair, are currently beyond the capability of most surgeons in an acute setting. If a stent graft is selected, its diameter should be 110% to 115% of the normal aorta to allow for secure fixation. A variety of off-the-shelf aortic cuffs are available and their successful use has been reported in conjunction with thoracic aortic transection.

OPEN REPAIR OF THE SUPRARENAL INFERIOR VENA CAVA

Open repair of injuries to the suprarenal vena cava is one of the most difficult of all abdominal vascular operations. Exposure of the infrahepatic suprarenal IVC is achieved by an extended Kocher maneuver and right medial visceral rotation. One cannot overemphasize the utility of intravascular balloon control in these cases to avoid hemorrhage. Balloon control can be combined with external pressure and the application of partial occlusion clamps to provide hemostasis. Fine Allis clamps are useful in coapting and controlling the cut ends of the IVC and are preferable to more traumatic attempts at control. Wounds of the infrahepatic suprarenal IVC are usually managed by
lateral venorrhaphy with running vascular suture. Narrowing the IVC 50% to 60% is often acceptable. If lateral venorrhaphy is not possible, patch repair using prosthetic or biologic material is acceptable. The use of anticoagulation in these circumstances is unsettled and is likely to remain individualized. Ligation of the suprarenal IVC should be avoided. Injuries to the retrohepatic vena cava, especially those that accompany blunt trauma, usually involve avulsion of the hepatic veins. Such injuries are highly lethal. Exposure of the retrohepatic IVC involves mobilization of the liver and anterior medial rotation of the right lobe. Repair of retrohepatic venous injuries may require hepatic isolation (control of the aorta at the hiatus as well as the vena cava above and below the injury and occlusion of the portal triad), placement of an intraluminal shunt between the right atrium and infrarenal IVC or venovenous bypass with hepatic isolation. These techniques are only used in desperate circumstances when bleeding persists despite adequate perihepatic packing. In general, injuries in this area should initially be treated by packing, nonexpanding hematomas should not be opened, and the extent of injury should be defined and definitive repair planned after the patient has been stabilized.

**ENDOVASCULAR TECHNIQUES IN THE SUPRARENAL IVC**

At this point, any endovascular approach would be considered experimental. The complexities of and poor results with open surgery in this area make an endovascular approach to suprarenal IVC injuries an attractive potential alternative. Remote access and control, facilitating exposure, along with limited occlusion of the IVC, are all points in favor of an endovascular approach. The size and distensibility of the IVC complicate the selection of an appropriate diameter endovascular graft. Patients with caval injury are often in shock and there may be external pressure on the vessel, both factors that cloud the estimation of caval diameter. No stent grafts have been made for caval use, and it is likely that aortic cuffs or short segment of grafts used for thoracic aortic repair would be most useful. Inadvertent coverage of the renal or hepatic veins represents a further potential complicating factor. There have been no reports of endovascular treatment of hepatic vein injuries. Nonetheless, the potential treatment of these injuries by remote rather than
direct access is appealing enough that it will undoubtedly be investigated in the future.

**REPAIR OF THE INFRARENAL AORTA AND ILIAC ARTERIES**

Injuries to the infrarenal aorta and iliac arteries can be managed by a combination of open and endovascular techniques. Use of an endovascular balloon to achieve proximal arterial control, described for ruptured aortic aneurysm, should be considered as a part of management. These techniques require access to intraoperative fluoroscopy and familiarity with endovascular techniques. The balloon should be placed in the operating room before celiotomy if possible, either through the femoral artery with a supporting sheath or the left brachial artery, as previously described.\(^3\)\(^4\) The balloon does not need to be inflated if the patient remains stable. Because concurrent visceral injury is common, laparotomy is almost universally required. After “damage control” of any gross intestinal spillage, attention is turned to the arterial injuries. Exposure of the aorta and iliac arteries has been described. When there is minimal enteric spillage, irrigation and repair with an in situ prosthetic bypass of appropriate diameter is the most expeditious approach. The repair should be wrapped in omentum if possible to separate it from the viscera. In the presence of significant contamination, the infrarenal aorta and/or iliac vessels should either be repaired primarily, ligated, or a temporary shunt inserted as part of a “damage control “strategy.”\(^42\) If ligation is required, extra-anatomic (eg, axillofemoral or femoral) bypass with prosthetic material can be used to restore perfusion to the lower extremities. If the aortic bifurcation is preserved, a unifemoral bypass is possible. In cases where the aortic bifurcation is not salvageable, primary end-to-end anastomosis of the proximal ends of the common iliac arteries can be performed, followed by axillo-unifemoral bypass. If this is not possible, axillo-bifemoral bypass may be required.

Unilateral common iliac artery injuries may be ligated with subsequent cross femoral reconstruction using a prosthetic graft. Isolated external iliac artery injuries can be repaired in most cases with saphenous vein interposition. Internal iliac artery injuries should be ligated. In the absence of significant contamination, interposition graft replacement of the damaged
vessel with a prosthetic graft is preferred. There are advocates of in situ prosthetic bypass, even in the face of more significant contamination.\textsuperscript{52} We prefer not to do this unless the situation is life threatening and prefer temporary placement of a shunt.

Endovascular repair of injured aorta and iliac vessels can be performed using techniques applied for repair of endovascular infrarenal aortic aneurysm repair. One must remember, however, that many of these patients are young and the durability of these repairs is unknown. In addition, most patients will require laparotomy for associated injuries. These 2 factors suggest a limited role for stent grafts in the treatment of traumatic lesions of the abdominal aortoiliac segment, as opposed to the more common use of stent grafts in traumatic rupture of the thoracic aorta. Endovascular repair has been used in treatment of traumatic dissection of the aorta or iliac arteries.\textsuperscript{53}

As previously noted, endovascular balloon tamponade is a valuable technique and endovascular coil embolization of difficult-to-access hypogastric artery branches can be employed with great success.

**INFRARENAL IVC AND ILIAC VEIN**

The principles of controlling venous injuries, including use of balloon tamponade and external pressure, have been previously described. The infrarenal IVC, iliac confluence, and right iliac vein are exposed through a right medial visceral rotation (see Fig. 20-8). The confluence of the iliac veins is obscured by the aortic bifurcation and right common iliac artery. If the aortic bifurcation cannot be sufficiently mobilized to provide exposure, the right common iliac artery should be mobilized or even transected for additional exposure. This is often required in any event because concomitant arterial injury is common. The more distal left iliac vein is approached on either side of the descending/sigmoid colon depending on the location of the injury.

As with the suprarenal IVC, lateral venorrhaphy is the preferred approach, with autogenous vein patch or ligation as alternatives. If needed, the infrarenal IVC and iliac veins can be ligated, due to the rather extensive collateral network that can develop within hours. While this may cause fluid sequestration in the lower legs, it is usually tolerated in the short term and is preferable to an attempt at repair in an unstable patient. In the rare case that
Ligation results in extreme distal venous hypertension, a bypass graft is indicated. In patients who have been stabilized, we prefer venous repair, either with a vein patch or, when an interposition graft is required, a ringed prosthetic conduit. Successful venous repair must use a conduit of equal or slightly greater diameter than the native vein and should avoid any tension. Saphenous vein is of insufficient diameter for replacement of the iliac vessels and must be modified to be useful (“panel” grafts”). We find such panel grafts excessively time-consuming to construct in these critically ill patients and prefer externally supported PTFE of suitable diameter and length. This is usually done in situ but may be performed using an extra anatomic route. When short segments of prosthesis are used in the presence of distal venous hypertension, flow is usually sufficient to maintain patency without the need for anticoagulation or an adjunctive fistula. In our experience, when thrombosis of a prosthetic vein graft does occur, adequate collateral venous flow has invariably been present. The indication for caval filters in patients with venous injury is not clearly established and remains a manner of individual clinical judgment.

**TREATMENT OF TRAUMATIC ARTERIOVENOUS FISTULA**

Fistula between the major arteries and veins can occur at any level, because the vessels are in close proximity throughout their course. It is important to realize that, while this may occur acutely, such a fistula rarely represents a true vascular emergency. Exsanguinating hemorrhage does not occur, because the arterial blood is decompressed into the venous system. Most of these patients present months to years after their initial injury. These patients may present with a continuous bruit, signs of lower extremity edema, and high-output cardiac failure. Management depends on an accurate history of trauma, including prior surgery (particularly lumbar disc surgery) or endovascular manipulation. Detailed vascular imaging is essential. These patients are rarely in extremis, and an effort to delineate the problem and develop a careful plan of correction is time well spent. Repair can usually be delayed until the patient is stabilized and other acute problems are corrected.

Treatment is directed at repair of both the arterial and venous defects. This is most often done by primary suture closure, although patch closure is
sometimes required. Proximal and distal arterial control is essential and is obtained using open or endovascular techniques as described previously. Proximal and distal venous control should be obtained when possible before opening the fistula. This can be done by external dissection, compression, or an intraluminal balloon. Central venous occlusion is important to prevent air embolization when the vein is opened. We generally avoid extensive venous dissection in close proximity to the fistula. On occasion, venous control can be obtained by placing a balloon catheter through the fistula from within the artery and then closing the communication with interrupted or running sutures. In the acute circumstance, the artery and vein may be separated, but this is more difficult in the case of a more chronic fistula and closure of the communication, by primary suture or patch, can be done from within the vessel. If this approach is chosen, it is important to be sure that the communication has been completely interrupted at the end of the procedure by use of intraoperative ultrasound or angiography. Appropriate flushing of both the arterial and venous sides is important to avoid embolization of debris or air into the central venous circulation.

Arterial-venous communications can also be approached endovascularly using covered stents. The stent can be placed only on the arterial side of the defect if the site of injury is in a main artery and can be accurately identified. However, it is important to remember that the arterial injury may be in a branch of one of the iliac vessels, in which case placement of a stent graft in the main artery will not correct the abnormality. Detailed description of repair of these branch fistulae is complex and beyond the scope of this chapter. Suffice it to say that coil embolization can be particularly dangerous in these cases due to the high flow in the venous system and chance of central venous embolization. A variety of techniques can be employed to reduce this possibility. Endovascular treatment of these lesions should only be undertaken by those with significant experience in endovascular techniques. As with open repair, it is important to be sure that complete interruption of the fistulous communications has occurred using completion angiography.

**TRAUMA TO THE MESENTERIC ARTERIES AND VEINS**

The origin of the celiac axis is exposed through the gastrohepatic ligament or
by a left medical visceral rotation as described earlier. While a short bypass from the aorta to the bifurcation of the splenic and hepatic arteries can be performed, the origin of the celiac artery can be ligated safely, if necessary, in most cases. This is preferable to attempting repair in a relatively confined space in an unstable patient. Collaterals through the pancreaticoduodenal and gastroduodenal are usually sufficient to preserve foregut flow. If there is any doubt, a bypass can be performed from the aorta to the common hepatic artery. The splenic artery can be ligated, as can the splenic vein. In the case of proximal injuries to the splenic vessels, the short gastric vessels provide adequate collateral flow. When the splenic vessels are injured close to the hilum, a splenectomy is usually the best approach. Injuries to the common hepatic artery may be ligated because of collateral circulation, while injuries to the proper hepatic artery are more likely to require repair. In order of preference, techniques are primary repair, interposition vein graft, and aortomesenteric graft using either saphenous vein or prosthetic. Two-thirds or more of hepatic flow is supplied by the portal vein, and, if this is intact, proper hepatic artery ligation is an acceptable option. Intrahepatic arterial lesions are generally treated with angiographically directed coil embolization unless massive exsanguination requires resection of the damaged area of the liver.

Injuries to the main trunk of the SMA should be repaired because significant loss of small bowel may result from sacrifice of the vessel. Ligation of proximal SMA aneurysms can be performed with acceptable results, due to the presence of collaterals from the celiac and inferior mesenteric arteries. However, in the trauma setting, integrity of collateral pathways from the pancreaticoduodenal and middle colic vessels is not easily ascertained and repair should be performed. Lesions at the origin of the vessel are best exposed by left medial visceral rotation and repaired with a short bypass originating from the aorta. More distal lesions are exposed through the base of the small bowel mesentery and can be repaired by patch angioplasty, interposition graft using saphenous vein, or proximal ligation and distal bypass arising from the aorta. In the trauma setting, the infrarenal aorta is preferred as inflow for the more distal SMA because supraceliac exposure and control is best avoided in patients who may be unstable and have multiple injuries. Saphenous vein is the preferred conduit. The details of SMA bypass have been described, including the need for proper length and orientation to prevent kinking. Trauma to the branches of the SMA is usually
treated by vessel ligation and any nonviable bowel is resected. Attempts to repair distal arterial and venous injuries in the mesentery are not rewarding. Mesenteric hematomas that are not expanding and are not associated with compromised bowel should be observed initially with angiography as necessary to identify vascular lesions. Attempts to explore stable mesenteric hematomas can lead to excessive blood loss and vascular compromise, resulting in more bowel ischemia.

Injuries to the splenic vein are treated by ligation, with or without splenectomy. There is often an accompanying injury to the splenic artery. In the rare instance of isolated splenic vein injury, consideration should be given to concomitant splenic artery ligation or splenectomy. Acute ligation of the splenic vein alone may result in sequestration of significant amounts of blood within the spleen and left-sided portal hypertension. This can be ameliorated by ligating the main arterial inflow to the spleen. Injuries to the main trunk of superior mesenteric vein should be repaired to avoid bowel ischemia secondary to mesenteric venous obstruction. If the vein cannot be repaired using a patch angioplasty or short interposition graft, a bypass from the superior mesenteric vein to the portal vein should be performed. This probably will require a large (6- to 8-mm) conduit of either reinforced PTFE or deep vein (jugular or femoral). Injuries to the portal vein should be repaired if possible, by lateral venorrhaphy, patch angioplasty, or interposition grafting, if the patient is stable enough to undergo repair. The retropancreatic portal vein is best exposed by transection of the pancreas (Fig. 20-15). Isolated injuries of the portal vein, with an intact hepatic artery, may be ligated if necessary to save the life of the patient, although significant hepatic dysfunction and acute massive bowel edema can be anticipated. This leads to significant fluid sequestration and may even result in bowel necrosis. Lesions of the hepatic artery and portal vein that are not immediately lethal should be repaired if possible.
FIGURE 20-15 Exposure of the retropancreatic portal vein by division of the pancreas.

Injuries to the inferior mesenteric artery can usually be ligated, because adequate collaterals will exist from the arc of Riolan, the marginal artery of Drummond, and the hemorrhoidal vessels. If it appears that ligation will not be tolerated, reimplantation, a short bypass with the saphenous vein, and ligation with resection of any ischemic colon are all acceptable alternatives.

INJURIES TO THE RENAL ARTERY AND VEIN
Management of renal artery lesions is dictated by the overall status of the patient, duration of ischemia, and presence or absence of a contralateral kidney. It is important to remember that after 60 minutes of warm ischemia time, most of the kidney’s excretory function is lost. While some authors advocate renal vascular repair within the first 3 to 6 hours after injury, preservation of long-term renal function in these cases has been poor. Therefore, situations in which there is nonvisualization of one kidney on a preoperative CTA or intravenous pyelogram (IVP) suggests that renal function will not be salvaged by revascularization. In most cases of arterial transection, ligation with nephrectomy is indicated. In cases of blunt trauma observation is usually indicated. In circumstances where the status of the kidney is unknown or when there is not a contralateral kidney, attempts at revascularization should be undertaken. The most expeditious approach is aortorenal bypass for lesions of the main renal artery, using saphenous vein with PTFE as a second choice. Lesions of the more distal renal artery, at or beyond branch points, are best ligated in the acute situation, unless they can be repaired with a simple vein patch, or if the injury is to a solitary functioning kidney. If there is doubt about contralateral renal function, the ipsilateral (damaged kidney) ureter can be clamped and indigo carmine administered intravascularly. Appearance of dye in the urine confirms contralateral kidney function. Renal artery thrombosis due to blunt trauma, diagnosed as lack of perfusion on CT scan, can be treated by endovascular placement of a stent if the patient is otherwise stable. However, salvage of a renal vessel in a patient with a contralateral functioning kidney remains a secondary priority in the trauma patient’s overall management.

Lesions of the proximal renal veins may be ligated, as long as collateral flow through the gonadal, adrenal, and hypogastric veins is preserved. This works best on the left side. While it is known that some transitory renal dysfunction will occur after renal vein ligation, it is generally well tolerated. If inadequate venous collaterals exist or have been damaged during the course of the injury, a short bypass between the renal vein and the vena cava with 8- to 10-mm PTFE can be performed, although ligation and nephrectomy is appropriate if the patient is unstable. Under rare circumstances of injuries to the renal hilum, for example with a solitary kidney, nephrectomy with ex vivo repair and autotransplantation may be indicated. This extensive reconstructive surgery, however, is unwise in an unstable patient with a contralateral functioning kidney.
TREATMENT OF RUPTURED ABDOMINAL AND VISCERAL ANEURYSMS

In the patient presenting with abdominal pain, pathology of the abdominal aorta and its branches should always be included within the differential diagnosis. Because of their rapidly catastrophic potential, prompt diagnosis and timely treatment for ruptured abdominal aneurysms are mandatory for patient survival and a successful outcome. While the most common aneurysms of the abdomen involve the abdominal aorta and iliac arteries, aneurysms of the visceral vessels may also rupture and present as abdominal emergencies.

Ruptured Aneurysms of the Aorta and Iliac Arteries

Although historically called atherosclerotic aneurysms, the etiology of abdominal aortic aneurysms (AAAs) has come to be recognized as multifactorial. This complex interplay, which includes elastin degradation, increased proteolytic activity, inflammation, matrix metalloproteinases, and other factors, leads to the ultimate development of aortic expansion and degeneration. It is for this reason that the term degenerative aneurysm better describes the pathophysiology of AAAs. Familial and sex-linked factors also likely contribute: the incidence is several times higher in men, and the relative risk for development of AAA among first-degree relatives of affected individuals is increased 11-fold. The infrarenal aorta is the most common intra-abdominal location for aneurysmal degeneration; aneurysmal degeneration of the suprarenal aorta is much less common.

Despite advances in treatment and early diagnosis, AAAs continue to be a significant cause of death. In the United States, AAAs are the 15th cause of death overall and the 10th leading cause among men older than 55 years. With improvements in the operative and perioperative management of elective AAAs, coupled with the introduction and refinement of endovascular techniques, ruptured AAAs overwhelmingly account for most of these deaths. Even among specialized centers, the operative mortality for ruptured AAAs remains high, between 35% and 50%, a range that has remained
constant over the past 3 decades. When one also considers the proportion of patients who die without reaching the hospital, the mortality rate approaches 75%. Accordingly, and because AAAs are notoriously asymptomatic until ruptured, much clinical research has centered on the natural history of the disease, specifically focused toward identifiable risk factors for rupture.

The absolute diameter of the aneurysm is the principal determinant of rupture risk. As the diameter increases, the risk of rupture increases nonlinearly, such that larger aneurysms have a significantly higher rupture rate. For example, AAAs 5 to 5.5 cm have an annual rupture risk of less than 5%, whereas those 6 to 7 cm in diameter have a 10% to 15% annual risk of rupture. These “hinge points,” in which the rupture risk rises dramatically, are the basis for recommending elective repair for asymptomatic AAAs based on size alone (in general, >5.5 cm in average-risk patients). Several other factors also independently predict rupture risk. The strongest risk factors are hypertension, chronic obstructive pulmonary disease (COPD), and family history of AAA. Other possible risk factors include rapid expansion (>0.4 cm annually), female gender, and current smoking history.

The classic presentation for ruptured AAA is abdominal or back pain, pulsatile mass, and hypotension; however, this complete triad is present in only a minority of patients. A large pannus or abdominal girth may preclude appreciation for a pulsatile mass; similarly, a blood pressure of 100 mm Hg systolic in an otherwise hypertensive individual may be mistakenly interpreted as “normotensive.” Pain is almost always a presenting symptom, and may include abdominal or back pain, groin pain, testicular pain, or flank pain. Less commonly, a patient with a large ruptured AAA may be obtunded and can present with hypotension only. The diagnosis of ruptured AAA must be included among the differential in every patient older than 50 years presenting with abdominal pain, abdominal pain and hypotension, or hypotension alone. When a pulsatile mass is also appreciated, the diagnosis of ruptured AAA is almost certain.

Much less commonly, an aortocaval fistula may arise from rupture into the adjacent IVC; signs and symptoms may include a bruit, distended veins, and acute heart failure. In general, these patients may be hypotensive but can usually be resuscitated. Because their treatment is different from that of a ruptured aneurysm, careful examination of the abdomen, with an effort to identify a thrill or bruit, will help in diagnosis.
DIAGNOSTIC IMAGING

Ultimately, the role of imaging should depend on the patient’s hemodynamic stability. Diagnostic imaging should not delay treatment. In the patient with abdominal pain and hypotension and a pulsatile abdominal mass, immediate transport to the operating room without imaging may be appropriate. In the more stable patient, in whom the diagnosis is in question, abdominal ultrasound or expeditious CT scan may be performed rapidly in the emergency room to identify AAAs. When performed expeditiously by an experienced ultrasonographer, the diagnosis of ruptured AAA may be rapidly confirmed sonographically. However, the technique is operator-dependent and accuracy may be limited by excessive bowel gas and obesity.

CT scanning is the most accurate and useful radiographic method in the evaluation of ruptured AAA (Fig. 20-16). The most common findings are retroperitoneal hematoma, an aneurysmal aorta, and retroperitoneal stranding of blood. With 100% specificity and a very high sensitivity, CT can reliably confirm or rule out the diagnosis of ruptured AAA as well as identify alternative nonvascular causes of the patient’s symptoms. It also yields important anatomical information about adjacent structures (such as a retroaortic left renal vein, horseshoe kidney, or concomitant iliac aneurysms) and about the aneurysm itself (such as an inflammatory AAA). CT scanning is particularly important if endovascular repair is contemplated. The newer-generation multislice scanners allow for complete chest and abdominal imaging to be completed in less than 5 minutes. Although intravenous contrast is very helpful in the planning for elective AAA repair, it is not required for diagnosis in the patient with suspected rupture and may exacerbate postoperative renal dysfunction. Even with an endovascular approach, thin slice (2 mm) noncontrast CT can provide sufficient information for repair.
PREOPERATIVE MANAGEMENT

Once the diagnosis of ruptured AAA is made, either by clinical presentation or radiographically, the patient should be taken immediately to the operating room. Large-bore intravenous access in the upper extremities (or central venous access), indwelling urinary catheter, type and cross-match for at least 6 units of packed cells, and chemistry and coagulation studies should all be performed. Because elevated blood pressure may lead to frank rupture of an otherwise contained leak, a strategy of permissive preoperative hypotension with minimal fluid resuscitation has been recommended. Although no rigid blood pressure parameter exists, most vascular surgeons would favor a minimum systolic pressure to maintain consciousness (usually around 80 mm Hg systolic).

OPEN REPAIR

Open repair remains the most common and versatile approach to ruptured AAA. Because general anesthesia will lead to both generalized vasodilatation
and relaxation of the abdominal musculature, both of which can produce abrupt hypotension; the patient must be prepped and draped (“nipples to knees”) and the surgical team scrubbed prior to induction. A cell saver device should be set up and used when possible. A midline incision is performed for rapid access to the suprarecial aorta. In recent years, transfemoral placement of an occlusion balloon in the suprarenal aorta prior to induction of anesthesia has been proposed to facilitate rapid aortic control should the patient become hypotensive on induction. Although this is a useful adjunct, it does require imaging capability in the operating room. After induction, the abdomen is opened from xiphoid to pubis. The abdomen and retroperitoneum are inspected. If a small or moderate retroperitoneal hematoma is found without intraperitoneal blood, the suprarecial aorta is controlled, as described earlier, but the artery is not clamped. If the juxtarenal aorta is spared of hematoma, this area may be dissected and a clamp applied directly below the renal arteries. Should bleeding develop during the course of this dissection, the suprarecialia clamp is applied.

If intraperitoneal blood is present, rapid suprarecial aortic control is obtained, usually by manual compression at the diaphragmatic hiatus while the anesthesiologist rapidly continues resuscitation. The suprarecial aorta is then exposed as previously described and occluded with a vascular clamp. Once the cross clamp is placed, the distal aorta is palpated to confirm obliteration of the pulse and attention is turned to the aneurysm. In patients with massive rupture, bleeding, or hypothermia, in which coagulopathy is almost certainly present, heparin is not given. In such cases, thrombectomy of the distal vessels and vigorous flushing of the graft are necessary prior to restoring flow. In all other cases, we give a small dose of heparin, 40 to 50 U/kg.

There is an increasing tendency to obtain intravascular suprarecial balloon control of the aorta prior to celiotomy. There is data that suggests this is superior to open aortic cross clamping. This is performed by passing a wire and then a balloon into the suprarecial aorta via either a retrograde transfemoral or a prograde transbrachial approach, as described earlier in the chapter, before induction of anesthesia. This requires intraoperative fluoroscopic capabilities and catheter/guidewire skills. This approach provides less invasive and more rapid control of the suprarecial aorta and can facilitate resuscitation of the patient in circumstances of profound shock.

The aneurysm is approached by evisceration of the transverse colon and
omentum cephalad and the small bowel to the right. Care is taken not to injure the IVC or the inferior mesenteric, gonadal, or left renal veins. In most cases, the retroperitoneal hematoma facilitates the dissection. Efforts are made to identify an infrarenal neck of the aneurysm and place a clamp at this level. When there is a free rupture of the aorta, the surgeon can pass the fingers of one hand through the rupture into the aorta (after application of the supraceliac clamp) to help locate the proximal neck of the aneurysm. Bimanual palpation can facilitate the placement of a clamp above the aneurysm without extensive dissection. Once the aortic neck is controlled, the iliac vessels are dissected to allow for clamping and control. Because the iliac veins often adhere to the artery, circumferential dissection around the iliac arteries should be avoided to prevent vein injury. In most cases, the iliac arteries may be readily clamped with minimal dissection. However, if the dissection is difficult, as with a large distal hematoma, endoluminal control may be obtained using a number 5 occlusion balloon, placed in each iliac artery after opening the sac. Once the aneurysm has been isolated proximally and distally, the sac is opened longitudinally and thrombus evacuated. Bleeding from the lumbar vessels is controlled with direct suture ligation using a mattress suture (Fig. 20-17). Venous bleeding encountered inside the sac suggests an aorto caval fistula. In those cases the patient should be placed in mild Trendelenburg’s position to reduce the chance of air embolus and the venous bleeding controlled by pressure. The defect is oversewn from within the aneurysm sac, with gentle digital or spongestick compression of the cava proximally and distally (Fig. 20-18). No attempt is made to clamp or mobilize the cava.
FIGURE 20-17 Control of lumbar vessels from within the aneurysm using mattress sutures to encircle the vessel.
FIGURE 20-18 Repair of an aortocaval fistula from within the aneurysm. Venous back bleeding is controlled with sponge sticks. This avoids dangerous dissection of the vena cava.

Because of the significant risk of colon ischemia following ruptured AAA repair, reimplantation of the IMA should be considered in cases of ruptured AAA.\textsuperscript{79} Brisk back bleeding suggests adequate SMA collaterals and implantation is not required. If the IMA is \textit{patent} and back bleeding is absent or sluggish, reimplantation of the IMA should be planned after aortic repair. In these cases, the IMA is controlled just outside the aneurysm sac with a small bulldog clamp, and after the aortic repair the IMA is reimplanted on the
aortic graft using a Carrel spatulated patch. An IMA that is obviously occluded at its origin is not reimplanted.

With the aneurysm opened and bleeding controlled, the graft may be sewn in place. When possible, this is done with an infrarenal clamp in place. It is absolutely mandatory that the proximal anastomosis be sewn meticulously into relatively healthy (nonaneurysmal) aorta. Poorly placed sutures in friable aorta will lead to proximal suture line bleeding once clamps are removed. If a secure anastomosis cannot be performed with an infrarenal clamp, the proximal anastomosis should be done with a suprarenal clamp in place. Tamponade of visceral back bleeding may be required while this is performed by placing an inflated balloon catheter through the aneurysm neck into the visceral aorta. Sutures must be placed in the aorta precisely and without tension or torsion of the needle. The proximal anastomosis may be reinforced with a Teflon felt pledget. Once the proximal anastomosis is completed and judged to be satisfactory, heparinized saline (5000 U/1000 mL saline) is flushed into the graft and the graft clamped. The distal anastomosis is then performed in a similar fashion. If heparin had not been given, a number 4 balloon thrombectomy catheter is gently passed down each iliac artery to extract thrombus. The graft should also be flushed to ensure adequate forward flow and the anastomosis is then completed (Fig. 20-19).
The anesthesiologist should be notified before release of the distal clamps. One leg should be perfused gradually, once the pressure has stabilized, the contralateral leg may be perfused. Pulses are checked at the femoral level and should be palpable; if not, thrombus or emboli are likely present and should be treated with thromboembolectomy. With the blood pressure stabilized and following a period of adequate perfusion, both feet should be assessed. Although palpable pulses may not be present, the feet should appear viable with reasonable capillary refill with Doppler flow.
Once adequate perfusion to the lower extremities has been achieved, the colon should be assessed. The colon should appear pink and Doppler flow should be present ideally at the antimesenteric border. If the colon appears ischemic, IMA reimplantation should be performed if not already done.

Hemostasis should be assured as best as possible prior to closure, and this may require infusion of additional clotting factors and protamine if heparin were given. The aneurysm sac is closed snugly around the graft with a running suture to obliterate the dead space and provide some hemostasis. The intestines should be excluded from contact with the graft as best as possible, usually by closing the proximal retroperitoneum or occasionally with a mobilized segment of omentum.

If the abdomen can be closed without tension, the linea alba is approximated and closed with a running suture. However, in many cases, the substantial hematoma precludes closure, and to prevent the development of abdominal compartment syndrome, the abdomen is left open with subsequent delayed closure several days later.

**ENDOVASCULAR REPAIR**

Endovascular repair for ruptured AAA (rEVAR) was first reported almost 2 decades ago. The early reports of decreased morbidity and mortality have been duplicated in other large single-institution series and large database reviews, with mortality rates for ruptured AAA ranging from 20% to 35%, compared with historical death rates for open repair of 50% or greater. However, three prospective randomized trials have failed to show a benefit of rEVAR over open repair, with mortality rates slightly, but not significantly, lower in the rEVAR group, although one did show improved long term outcomes and cost effectiveness in the rEVAR group. A meta-analysis of open and endovascular approaches to ruptured AAA showed that the benefit of rEVAR was lost when adjustments were made for the hemodynamic condition of the patient at the time of surgery. It is important to note, however, that rEVAR was equivalent to open surgery in each of those trials and superior to open surgery in cases that were selected as suitable by the operating surgeon based on anatomic characteristics and hemodynamic stability. In addition recent large data base studies suggest superiority, particularly in elderly patients. Therefore, it appears that rEVAR will have a place in the management of patients with ruptured AAA. It is currently
used in about one-third of patients with ruptured AAAs in the United States, and there is reason to expect that this percentage might increase to 30% to 50% in the future.

Successful endovascular repair of a ruptured AAA requires a dedicated team with experience in rEVAR for routine aneurysms, rapid imaging and triage by the emergency ward, 24-hour availability of imaging in the operating room, and a suitable stock of endografts. When these are in place, improvements in mortality can be expected in appropriately selected patients. It is important to note that rEVAR is associated with an increased risk of abdominal compartment syndrome, since the abdomen is not routinely entered with this technique and ongoing bleeding may be expected from lumbar and IMA back bleeding (type II endoleak) that may not be tamponaded in the absence of an intact aortic wall. Abdominal compartment syndrome may be seen in up to 20% of patients after rEVAR and can be diagnosed by increased bladder pressures (>20 mm Hg), increased peak airway pressures with difficulty in ventilation, and reduced urine output. Treatments is laparotomy with decompression and control of any bleeding source.

The single most important consideration is the ability to expeditiously proceed with endovascular aortic control and suitable repair in the patient with a ruptured AAA before irreversible shock occurs. Multiple centers have described their techniques and operative strategy, and some variation exists; however, the fundamental principles are identical to our center’s technique. The preoperative management and anesthetic considerations are the same as for open repair. Data have emerged indicating that endovascular balloon control, obtained under local anesthesia, reduces operative mortality, and this is preferred when possible. In most cases, the repair is completed under general anesthesia to facilitate control of the patient’s airway and minimize motion.

Access is obtained through both femoral arteries simultaneously. One artery may be accessed percutaneously with placement of a closure device. Once access is obtained by a Seldinger technique, bilateral 6-Fr sheaths are placed over floppy wires and subsequently exchanged for a stiff wire over a guiding catheter to the level of the proximal descending aorta. Contralateral to the side proposed for deploying the main body of the graft, the sheath is exchanged for a large sheath and a compliant 45-mm aortic balloon is introduced to the level of T12. Although a 12-Fr sheath is the minimum size
for the compliant aortic balloon, we prefer larger sheaths to allow for simultaneous pigtail catheter placement. If the patient is hemodynamically stable, the procedure can proceed with the balloon in place but not inflated. A marking pigtail catheter is introduced over a second floppy wire, aortogram is performed, and the position of the renal arteries marked. The main body graft is then introduced through the opposite femoral artery over the stiff wire and placed in appropriate position (Fig. 20-20). The deflated aortic balloon and its sheath are pulled back and the graft is deployed as is normally done for an elective rEVAR. The ballon is then removed from the contralateral limb and inserted through the main body of the graft into the suprarenal aortic position. The contralateral gate of the graft is then cannulated, and the contralateral limb is introduced and deployed. If the patient becomes unstable, the aortic occlusion balloon may be inflated in the suprarenal aorta.
The ipsilateral limb deployment is then completed and any ipsilateral limb extensions (if needed) are introduced and deployed. Once the endografting has been performed, all fixation sites are molded with the compliant balloon and a completion aortogram performed to document absence of endoleak (Fig. 20-21). A type I (attachment or perigraft leak) or type III endoleak (modular disconnection) warrants further repair before leaving the operating room, whereas a type II (branch endoleak) or type IV (graft porosity)
endoleak may be followed conservatively. All patients are watched closely for the development of abdominal compartment syndrome.

**FIGURE 20-21** Completed endograft for ruptured abdominal aortic aneurysm (AAA) showing complete exclusion of the aneurysm.

The femoral arteries are then closed primarily. If heparin had not been administered, inflow and back bleeding should be assessed prior to closure, and, if judged to be poor, a thrombectomy catheter may be passed gently to retrieve thrombus.

Although the above describes one approach for rEVAR, multiple options
exist, and the surgeon should be well acquainted with the options based on anatomic criteria should an endovascular approach be undertaken. These may include conversion to an aortouniiliac device with a femoral-femoral crossover graft or a proximal aortic extension in the case of a type I endoleak. It is anticipated that the future generation of endografts, along with greater surgeon experience, will lead to greater use of rEVAR for ruptured AAA.

**Results**

Although some variation exists among individual series, pooled data suggest an overall perioperative mortality of approximately 50% after open repair for ruptured AAA. Attempts have been made to correlate both pre- and postoperative variables with the probability of survival. Poor prognostic preoperative predictors include hypotension on induction (systolic blood pressure <90); age over 80 years, preoperative cardiac arrest, and low hematocrit. Similar logistic regression analysis has identified postoperative myocardial infarction, respiratory failure, coagulopathy, and renal dysfunction as strong predictors of postoperative mortality; the probability of survival decreases dramatically with 2 or more complications or with the need for dialysis.

Studies suggest that 40% to 60% of patients with ruptured AAA may be treated by endovascular means. As noted at the beginning of this section, rEVAR is associated with reduction in operative and hospital mortality of 20% to 30% in patients who are acceptable candidates for this approach. While it is unlikely that rEVAR will be applicable to all patients with ruptured AAA, up to 60% of patients may qualify for rEVAR in dedicated centers. It is likely that increased dissemination of this technology will lead to a global decrease in the mortality from ruptured AAA.

**Visceral Artery Aneurysms**

Aneurysms of the visceral arteries are uncommon, seen in 0.01% to 0.02% of autopsy studies. However, the increased utilization of routine body imaging has resulted in greater recognition and discovery of asymptomatic visceral artery aneurysms, and thus their true prevalence is likely higher. The elective treatment of visceral aneurysms is outside the scope of this chapter. The
major complications of these aneurysms are rupture or distal embolization and prevention of these complications is the rationale for elective treatment. Recent reports on renal artery aneurysms suggest a low risk of rupture and slow growth, which has tempered previous enthusiasm for elective repair. Indications for elective repair are unsettled but may include size over 2 cm, associated renal artery stenosis, and poorly controlled hypertension. Ruptured renal artery aneurysm is a rare entity, the treatment of which is outside the scope of this chapter. The remainder of this section will consider the management of a ruptured splanchnic artery. Table 20-1 summarizes the relative frequency of these aneurysms, their estimated risk of rupture, and recommended treatment. Approximately 25% to 30% of splanchnic artery aneurysms are ruptured at the time of presentation and about one-third are associated with aneurysms elsewhere in the arterial tree. Endovascular techniques have been applied to elective and emergent treatment of splanchnic artery aneurysms with increasing frequency. In properly selected patients, these techniques, which include embolization and covered stents, appear to be associated with reduced mortality in the case of aneurysm rupture.

### TABLE 20-1: SPLANCHNIC ARTERY ANEURYSMS

<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency (%)</th>
<th>Risk of Rupture</th>
<th>Indications for Surgery</th>
<th>Type of Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenic</td>
<td>60</td>
<td>Low</td>
<td>Symptomatic; pregnant or childbearing age</td>
<td>Ligation; splenectomy; transcatheter embolization</td>
</tr>
<tr>
<td>Hepatic</td>
<td>20</td>
<td>High</td>
<td>Symptomatic; asymptomatic &gt;2 cm (or all)</td>
<td>Ligation (common hepatic); endoaneurysmorrhaphy with arterial reconstruction; endovascular stent graft or transcatheter embolization</td>
</tr>
<tr>
<td>SMA</td>
<td>6</td>
<td>High</td>
<td>All</td>
<td>Ligation (with revascularization if compromised bowel)</td>
</tr>
<tr>
<td>Celiac</td>
<td>4</td>
<td>High</td>
<td>All</td>
<td>Ligation; resection with revascularization; aneurysmorrhaphy</td>
</tr>
<tr>
<td>Gastric/gastroepiploic</td>
<td>4</td>
<td>Very high</td>
<td>All</td>
<td>Ligation</td>
</tr>
<tr>
<td>Peripancreatic</td>
<td>Rare</td>
<td>High</td>
<td>All</td>
<td>Transcatheter embolization</td>
</tr>
</tbody>
</table>

**Splenic Artery Aneurysms**

Splenic artery aneurysms are the most frequent visceral aneurysms (60%), are the only aneurysms with a female predominance (3:1), and have the lowest
risk of rupture. Splenic artery aneurysms have the lowest risk of rupture, perhaps no more than 10% overall and less than 2% in low-risk patients. However, the risk of rupture rises dramatically among pregnant patients, with maternal and fetal mortality rates of over 70%, and after liver transplantation,\textsuperscript{101} which is the rationale for recommending repair of asymptomatic aneurysms in these groups.\textsuperscript{102} Both arterial medial dysplasia (more common in females) and the underlying vascular effects of multiple pregnancies (both hormonal and hemodynamic) have been proposed as contributing factors.\textsuperscript{103} Other possible etiologies include portal hypertension and splenomegaly, pancreatitis or pseudocyst-associated local inflammation, and trauma. Ruptured splenic artery aneurysm initially presents with abdominal pain referable to hemorrhage in the lesser sac without abdominal distention or shock. These signs may become apparent later after continued hemorrhage spills into the peritoneal cavity through the foramen of Winslow (“double rupture”).

In most cases, ruptured splenic artery aneurysms are treated by laparotomy and ligation. Restoration of arterial continuity is rarely necessary because of the collateral supply to the spleen, and therefore either open or endovascular obliteration of the aneurysmal segment is appropriate. Operative repair of proximal and midsplenic artery aneurysms entails exposure through the lesser sac, proximal and distal control, and simple ligation of the aneurysm without arterial reconstruction. It is important to ligate all feeding vessels; this may require opening the aneurysm and ligation from within the sac. Aneurysms of the splenic hilum require mobilization of the spleen and may be treated by ligation of all branches or splenectomy, if necessary. As in trauma, early control of the proximal splenic artery is important for the treatment of hilar aneurysms. While laparoscopic techniques have been reported for the elective resection of splenic aneurysms,\textsuperscript{104} they have no place in the acute setting. Endovascular approaches have been used with increased frequency and are particularly useful in patients at high operative risk, including those with contained rupture, pancreatitis, advanced portal hypertension, or liver transplantation. In these cases, if the patient is stable, vascular access to the splenic artery is obtained through the celiac artery from a femoral or brachial approach. Using guiding sheaths and microcatheters, the splenic artery is engaged and coils are placed distal to the aneurysm, in the aneurysm sac and then proximal to the aneurysm. There is a 10% to 15% risk of rebleeding\textsuperscript{105} using endovascular techniques, as well as a risk of splenic infarction when
hilar aneurysms are treated. However, the difficulties of open surgery in patients with pancreatitis or advanced liver disease justify attempts at endovascular treatment as a first effort. Endovascular stent graft placement has also been described\textsuperscript{106} and may be particularly useful in certain subsets, such as patients in whom preservation of splenic blood flow need be maintained (as for portal-systemic shunts) or in high-risk patients with pancreatitis-associated aneurysms and severe inflammation.

**Hepatic Artery Aneurysms**

Hepatic artery aneurysms, unlike splenic artery aneurysms, occur more frequently in men. There is some evidence that posttraumatic hepatic artery aneurysms are increasing in frequency. Etiologies include medial degeneration, atherosclerosis, trauma (up to 20\% of cases), infection (usually secondary to illicit drug use), vasculitis, and as a consequence of orthotopic liver transplantation.\textsuperscript{107} Hepatic artery aneurysms have a rupture risk of no less than 14\%\textsuperscript{107} and possibly higher.\textsuperscript{108} About half the ruptured hepatic artery aneurysms present with signs and symptoms of intraperitoneal hemorrhage, while the other half will rupture into the biliary tract, manifesting as either hemobilia or gastrointestinal hemorrhage.

A variety of treatment options exist for hepatic artery aneurysms, including ligation, excision, repair with arterial grafting and reconstruction, hepatic resection, and endovascular approaches.\textsuperscript{95,107–109} Treatment of ruptured hepatic artery aneurysms generally depends on their location and the status of hepatic blood flow. When feasible, preoperative arteriography is helpful in planning the operative approach. Arteriography can provide information on the collateral flow to the liver, demonstrate anomalies such as a replaced right or left hepatic artery, and identify multiple aneurysms, especially in the case of intrahepatic lesions.

Ruptured common hepatic artery aneurysms are treated by simple ligation and exclusion, unless the liver appears ischemic after clamping. Embolization of select common hepatic aneurysms may be considered in patients with a patent portal vein and good hepatic function. Collaterals from the right gastric and gastroduodenal arteries will maintain hepatic artery flow in most cases. Arterial reconstruction is indicated for most aneurysms of the proper hepatic artery and its extra hepatic branches unless the patient is too unstable to
tolerate attempts at bypass. In most instances, this requires interposition grafting (preferably with autologous saphenous vein) aneurysmectomy, or endoaneurysmorrhaphy. Because of their proximity to the bile duct and portal vein, dissection of the more distal hepatic or extrahepatic branch arterial aneurysmal segments may be tedious, and proximal and distal control may be easier from within the aneurysm itself. Ruptured aneurysms may require concomitant control at the supraceliac aorta level. If an interposition graft is not possible (as with distal common or proximal proper hepatic artery aneurysms), an aortohepatic bypass can be performed by exposing the right anterolateral border of the aorta through an extended Kocher maneuver and medial visceral rotation. The aortic anastomosis is performed first; the graft is tunneled retroduodenal to the porta hepatis and anastomosed to the hepatic artery after opening the aneurysm. If the patient is unstable, ligation of the hepatic artery, at any level, is acceptable as long as the portal vein is patent; the risk of hepatic infarction is low and is less than that of an extended procedure in a compromised patient.

Intrahepatic aneurysms are best treated by catheter-based embolization unless they are large. Options for endovascular treatment of hepatic artery aneurysms include both coil embolization and stent graft placement. Embolization has been most useful for small, saccular intrahepatic pseudoaneurysms, as may be seen following trauma or percutaneous biliary procedures with iatrogenic arterial injury. Large intrahepatic aneurysms may require liver resection. Endovascular approaches have also been described for extrahepatic aneurysms, including both coil embolization and the placement of endovascular covered stents.\textsuperscript{105}

**Superior Mesenteric Artery Aneurysms**

Superior mesenteric artery (SMA) aneurysms have been associated with an infectious etiology, dating back to DeBakey and Cooley’s 1953 report of successful resection of a mycotic aneurysm,\textsuperscript{110} and systemic infection (usually associated with endocarditis) continues to be a significant factor in their development. Other less common causes of SMA aneurysms include atherosclerosis, connective tissue disorders, vasculitis, and trauma. The risk of rupture of SMA aneurysms is in the range of 40% to 50%. The majority of SMA aneurysms occur in the proximal 5 cm of the vessel. SMA aneurysms are usually symptomatic, presenting with abdominal pain and sometimes
signs of intestinal angina. Treatment of ruptured SMA aneurysms is complicated by their frequent infectious etiology and difficulty with arterial reconstruction. Unlike the situation with trauma to the SMA, resection and reconstruction of aneurysms is often more difficult because the lesion is more extensive. While early teaching mandated proximal SMA reconstruction, larger, contemporary series suggest that ligation without revascularization can be considered in most patients. In these cases, test occlusion of the vessel to assess the extent of intestinal ischemia is critical prior to a decision on the need for reconstruction. When collateral circulation from the celiac and inferior mesenteric arteries, through the pancreaticoduodenal and middle colic vessels, respectively, is sufficient to maintain intestinal viability after test occlusion of the SMA, ligation can be performed. If extensive intestinal ischemia is present after test occlusion, bypass grafting is required. This is usually performed as an interposition graft or a bypass from the infrarenal aorta, using autogenous vein. More distal aneurysms of the SMA can often be treated by ligation with resection of the compromised small bowel as needed. Access to the origin of the SMA is obtained by left medial visceral rotation. The more distal segments of the SMA are exposed by elevating the mesocolon and dissecting through the small bowel mesentery, using the middle colic artery as a guide.

Transcatheter embolization is usually reserved for multiple small bleeding aneurysms in a hemodynamically stable patient. Assessment of bowel viability by angiographic determination of collateral flow and celiotomy is mandatory after the procedure is completed.

Celiac Artery Aneurysms

Medial degeneration is the most common etiology of celiac artery aneurysms. This is particularly true in those cases associated with anatomic anomalies such as a common celiomesenteric trunk. On occasion, aneurysmal dilation occurs distal to compression by the median arcuate ligament, although the incidence of rupture in these cases is unknown. Atherosclerosis is also associated with celiac aneurysms. Ruptured celiac artery aneurysms are usually treated by ligation, which is generally well tolerated. In saccular or very focal aneurysms, aneurysmectomy, and arterial reconstruction may be considered. In the patient with preexisting liver disease or evidence of
portal hypertension, reconstruction is indicated to maximally preserve hepatic nutrient flow. When necessary, arterial continuity may be established using either an aortoceliac bypass, originating from the supraceliac aorta or, less commonly, with an interposition graft. In some cases, the aneurysm may be confined to a portion of arterial wall; aneurysmorrhaphy may be accomplished with excision of that portion of aneurysmal wall provided the remaining wall is healthy. Exposure and control of the celiac artery is best obtained through a transabdominal incision and medial visceral rotation, allowing for visualization and subsequent division of the crura and median arcuate ligament. Alternatively, a direct approach through the lesser sac may be used.

**Gastric, Gastroepiploic, Gastroduodenal, Pancreatic, and Pancreaticoduodenal Aneurysms**

Gastric and gastroepiploic aneurysms represent 4% of splanchnic aneurysms, the majority of which are solitary and involve the gastric artery. The etiology is undefined but likely results from either medial degeneration or an associated inflammatory process. These aneurysms have a very high incidence of rupture, either into the peritoneum or the gastrointestinal tract, and 70% present with gastrointestinal bleeding. These aneurysms are best treated by ligation, including resection of involved organs as necessary. The excellent collateral supply of the stomach and the urgent nature of the operation make reconstruction inadvisable.

Aneurysms of the gastroduodenal, pancreatic, and pancreaticoduodenal arteries are usually associated with either acute or chronic pancreatitis. Occasionally these aneurysms are seen after liver transplantation or pancreaticoduodenectomy, particularly when complicated by postoperative pancreatic fistula. Most are symptomatic; rupture and gastrointestinal hemorrhage are common occurrences. Because of their association with pancreatic inflammation, gastroduodenal and pancreaticoduodenal aneurysms are best managed with transcatheter embolization and obliteration, especially in the setting of active hemorrhage.

**Aneurysms of Mesenteric Branches and the Inferior**
Mesenteric Artery

Jejunal, ileal, and colic branch aneurysms are usually small and often solitary. These aneurysms are often identified during angiography to investigate gastrointestinal bleeding or on CT scans for evaluation of abdominal pain. The presence of multiple mesenteric aneurysms suggests a systemic pathology such as polyarteritis nodosa, septic emboli from bacterial endocarditis, or a connective tissue disorder. Rupture is most commonly seen in aneurysms involving colonic branches. Rupture most often occurs into the mesentery, although free intraperitoneal rupture can occur. Management is operative ligation, with resection of involved bowel as necessary. Transcatheter embolization has a very limited role, because laparotomy is required in any case to assess intestinal viability.

Aneurysms of the inferior mesenteric artery are exceedingly rare and little is known about their etiology or natural history. These aneurysms can usually be managed by ligation, with revascularization using autogenous vein if collateral circulation is inadequate.

COMPLICATIONS AFTER RUPTURED ABDOMINAL AND VISCERAL ARTERY ANEURYSMS

Local and systemic complications are frequent after rupture of an abdominal aortic or visceral aneurysm. A high index of suspicion, prompt recognition, with early treatment of complications is mandatory for survival. Mortality rates range from 10% to 60% for ruptured visceral artery aneurysm and 40% to 75% ruptured aortoiliac aneurysms. Postoperative bleeding may occur as the result of ongoing coagulopathy (“medical bleeding”) or from a technical defect (“surgical bleeding”). Correction of hypothermia and coagulopathy (using blood component therapy) should be prompt, and abdominal reexploration, if bleeding continues, is mandatory. In the face of extensive blood loss and resuscitation, abdominal compartment syndrome may occur and should be promptly recognized. Abdominal compartment syndrome results in increased peak airway pressures, progressive hypoxemia, renal dysfunction and visceral ischemia from direct compression of mesenteric and hepatic capillary flow and venous compression, reduced cardiac output, and
increased intracranial pressure. The diagnosis is suspected on clinical grounds and confirmed by bladder manometry. Bladder pressures that exceed 20 mm Hg should be treated with decompressive celiotomy. Once the edema has resolved (usually within 7 days), the abdomen is closed, either primarily or with mesh.

Residual visceral ischemia may occur after resection of aortic or visceral aneurysms. Patients who have persistent fever, leukocytosis, or ileus after surgery should be evaluated for residual visceral ischemia, pancreatitis, or intra-abdominal abscess. This is particularly true when resection of abdominal organs has been performed. Colon ischemia occurs in up to 30% of patients after ruptured AAA repair, with an associated mortality of more than 50%. It occurs unpredictably, and can present with a range of signs and symptoms. Diarrhea, which may or may not be bloody, that occurs within 24 hours of AAA resection should raise suspicion of colonic ischemia; flexible sigmoidoscopy should be promptly performed in questionable cases. If the diagnosis of colonic ischemia is confirmed, differentiation between transmural and mucosal ischemia may be difficult, and the decision between nonoperative treatment (with broad-spectrum antibiotics, fluids, and bowel rest and repeat colonoscopy) or celiotomy and resection should be based on the patient’s clinical course. In questionable cases, it is better to err on the side of operative intervention and colon resection.

Rupture of the aorta or a major visceral vessel often results in shock and multisystem organ failure. Cardiac (myocardial infarction, heart failure, arrhythmias) and respiratory (respiratory failure, adult respiratory distress syndrome) problems predominate. Renal dysfunction occurs in about one-third of patients undergoing ruptured AAA repair; the need for dialysis portends a poor prognosis, with mortality rates of greater than 75%. Gastrointestinal and infectious complications may also occur, usually in the later stages of protracted convalescence. Finally, the culmination of these manifests as multisystem organ failure, which is the most common cause of death beyond 48 hours in patients with ruptured AAA.

Limb ischemia may be seen in patients after resection of ruptured AAA and is caused by distal embolization of aortic debris. If femoral or popliteal pulses are absent at the conclusion of surgery, prompt vascular exploration, usually by a groin incision, is indicated. In most cases the offending thrombus can be removed with an embolectomy catheter. If femoral and popliteal pulses are present, but pedal Doppler signals are diminished or
absent, more distal embolization has occurred. This sometimes manifests as “blue toes” and may be associated with microembolization of atherosclerotic debris to the buttocks, spinal cord, and sometimes abdominal and pelvic viscera. Treatment of this condition is generally supportive, because retrieval of microemboli is not feasible. Outcome depends on the severity and location of embolization and attendant ischemia and may range from full recovery to amputation and death.

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ESOPHAGUS
ESOPHAGEAL DIVERTICULA AND BENIGN TUMORS

Marco E. Allaix • Marco G. Patti

ESOPHAGEAL DIVERTICULA

Diverticula of the esophagus are a rare entity, with a prevalence that ranges between 0.06% and 4%.\(^1,2\) Esophageal diverticula are classified according to their location along the esophagus (pharyngoesophageal, midesophageal, or epiphrenic), and the mechanism of formation (pulsion or traction). Most common diverticula are those located in the pharyngoesophageal and epiphrenic locations. These are usually pulsion diverticula in which an increase of intraluminal pressure leads to herniation of mucosa and submucosa through the muscular layer resulting in a false diverticulum. Midesophageal diverticula are commonly traction diverticula. These are much less frequent and are the result of a focal traction of all layers (mucosa, submucosa, and musculature) of the esophageal wall by a periesophageal inflammatory process resulting in a true diverticulum.
Pharyngoesophageal Diverticulum (Zenker Diverticulum)

PATHOPHYSIOLOGY

Zenker diverticula are the most common diverticula of the esophagus. These arise in an area of muscular gap at the transition of the cricopharyngeal muscle and the inferior constrictors of the pharynx (Killian triangle) (Fig. 21-1), and are more frequently found on the left side of the esophagus due to the slight convexity of the esophagus to the left. Pathophysiologic mechanisms for this condition include muscular weakness and upper esophageal sphincter (UES) dysfunction. UES dysfunction is characterized by incomplete relaxation of the UES, increased intrapharyngeal pressure, and discoordinated pharyngeal contractions.\(^3\)\(^-\)\(^5\) Gastroesophageal reflux is present in up to 95% of patients and may be related to esophageal longitudinal muscle reflex contraction and consequent widening of the gap between pharyngeal constrictors and cricopharyngeal muscles\(^6\) or spasm of the UES.\(^7\)
Inferior constrictor muscle
Killian triangle
Esophageal diverticulum
Longitudinal fibers
FIGURE 21-1  Zenker diverticulum: anatomic and radiologic features. The radiologic image shows the presence of the pouch arising from the Killian triangle.

SYMPTOMS AND DIAGNOSIS

Cervical dysphagia is the most common presenting symptom and is often associated with regurgitation, halitosis, choking, chronic cough, hoarseness, gurgling, or aspiration pneumonia. Findings on physical examination may include the Boyce sign (a neck mass gurgling on palpation) and weight loss. The presence of progressive dysphagia, odynophagia, hemoptysis, and hematemesis is more suspicious for a malignancy and may be a squamous cell cancer arising from the diverticulum (incidence up to 1.1%).

Diagnostic tools include:

1. Barium esophagram is performed to assess size and location of the diverticulum and the size of the diverticular neck. In addition, it determines the distance from the diaphragm, therefore giving the surgeon the possibility of choosing between a laparoscopic or thoracoscopic approach.
2. Upper endoscopy is mandatory in order to rule out the presence of cancer or other esophageal diseases and to evaluate signs of reflux.
3. Esophageal manometry is important to define the underlying esophageal motility disorder. We usually obtain this test in all patients, even though some surgeons deem that it is not mandatory, in the belief that a primary esophageal motility is always present. The most common underlying disorder is achalasia, followed by diffuse esophageal spasm and nutcracker esophagus.

TREATMENT

Main indication for treatment is to address the patient’s symptoms from the diverticulum. The decision for intervention is made regardless of the size of the diverticulum, as it is mostly the underlying motility disorder that determines the symptom severity. However, some advice an operation also in the absence of symptoms to prevent the risk of aspiration.

Several treatment modalities directed at treating the motility disorder and
at managing the diverticulum have been proposed:

- Cricopharyngeal myotomy (CPM) alone
- CPM and diverticulectomy
- CPM and diverticulopexy
- CPM and diverticular inversion
- Diverticulectomy alone
- Diverticulopexy alone
- Diverticular inversion alone

In our experience, any procedure performed without a CPM results in an unacceptably high incidence of recurrent symptoms. Traditionally, these procedures have been performed through a left cervical incision. More recently, minimally invasive transoral endoscopic techniques have been developed.

**Open Transcervical Surgery.** This traditional approach is usually performed under general anesthesia, but can be accomplished with a cervical block and sedation. The diverticulum is either resected (diverticulectomy) or suspended and fixed to the prevertebral fascia (diverticulopexy), or invaginated into the esophagus.

In the past, *diverticulectomy* was performed with hand-sewn sutures, and was technically challenging with a risk of leak. The introduction of staplers has significantly reduced the risk of esophageal leak and mediastinitis (1.7%). Other risks of stapled diverticulectomy include recurrent laryngeal nerve injury, recurrence, and wound hematoma. Most surgeons advocate the addition of a CPM to the diverticulectomy.

*Diverticulopexy* consists of fixation of the sac of the diverticulum to the pre-vertebral fascia or pharyngeal muscles above the neck of the diverticulum. The advantage of diverticulopexy over diverticulectomy is that the hypopharyngeal mucosa is left intact, eliminating the risk of leakage, with shorter hospital stays.

*Diverticular inversion* is an alternative technique: the diverticulum is invaginated into the esophageal lumen and the neck is closed by using a purse-string suture. As for diverticulopexy, the hypopharyngeal mucosa is not breached. Hospital stay is shorter and complication rate lower after inversion.
The rationale of performing a CPM is to relieve the functional obstruction distal to the diverticulum, thus reducing the risk of esophageal leak following diverticulectomy and recurrence of the diverticulum. The CPM is also critical to relieving the symptoms. This procedure is performed by gently incising the cricopharyngeal muscular fibers until reaching the underlying hypopharyngeal mucosa. The extension of CPM is debated, but usually ranges between 3 and 6 cm below the cricopharyngeus muscle. Visualization of the muscular layers and mucosa may be enhanced by the placement of a bougie dilator in the esophagus prior to starting the myotomy. Perioperative complications include recurrent laryngeal nerve injury, pharyngocutaneous fistula, mediastinitis, and hemorrhage.

Currently, there are no randomized controlled trials comparing the different open approaches to Zenker diverticulum. As a consequence, the evidence supporting one approach over the other is limited. Small (1-2 cm) symptomatic diverticula can be safely treated with CPM alone, since most of these resolve after myotomy. The choice of surgical treatment for larger diverticula (2-4 cm) is not standardized and is left to the surgeon’s preference, but most commonly includes a CPM with diverticulectomy or diverticulopexy. To date, a diverticulectomy performed using staplers in association with a CPM is considered the approach of choice for diverticular larger than 4 cm since this is associated with very low fistula rates (1%-1.7%). Some would advocate resection to also eliminate the risk of cancer arising from the diverticulum.

**Endoscopic Transoral Surgery.** The goal of endoscopic transoral surgery is to sharply divide the common wall (septum) that separates the esophageal lumen and the diverticulum (diverticulotomy). A cricopharyngeal myotomy is automatically performed, since the common wall includes the cricopharyngeal muscular fibers. The first endoscopic approach to Zenker diverticulum with esophagodiverticulotomy was reported in 1917. It was then abandoned due to the high rates of mediastinitis and death, until 1960 when Dohlman and Mattsson demonstrated very low rates of mediastinitis rate and recurrence by using electrocautery.

Endoscopic diverticulotomy is accomplished under general anesthesia in patients with adequate oral access and the absence of both neck mobility
limitations and macroglossia. Endoscopic exposure is very limited in patients with a short neck, a short hyomental distance, and severe obesity, leading to a high rate of conversion to open surgery.\textsuperscript{18} In addition, endoscopic diverticulotomy may result in incomplete myotomy in cases of small (<3 cm) diverticula, since only a few muscular fibers are contained in the short septum.\textsuperscript{15,19,20} Some surgeons consider a very large diverticulum a contraindication to endoscopic diverticulotomy, since laser, argon plasma coagulation (APC), and diathermy are associated with higher risk of bleeding, and the use of several staple cartridges can lead to a higher risk of leak.

The endoscopic diverticulotomy can be performed by a flexible or rigid endoscope. Briefly, the endoscope is advanced down to the esophagus under direct vision until the septum is between the two valves of the endoscope. Four techniques have been described for the division of the septum for rigid diverticulotomy\textsuperscript{9}:

- **Electrocautery.** The overall morbidity (subcutaneous emphysema and mediastinitis) and mortality rates reported in the literature are about 8% and 0.2%, respectively. Electrocautery has been replaced by CO\textsubscript{2} laser and stapler techniques.
- **CO\textsubscript{2} laser.** This technique is associated with limited focal tissue trauma. The reported complications and mortality rates are 9.3% and 0.2%, respectively. Most common complications are subcutaneous emphysema, mediastinitis, fistula, and bleeding.
- **Linear stapler.** The main limitation of this approach is the size of the diverticulum: poorer outcomes are reported in patients with diverticula smaller than 3 cm. The overall morbidity rate is 7.1%, while death is reported in 0.3% of cases. Most common complications are dental injury, esophageal mucosal injury, and esophageal perforation.
- **Harmonic scalpel.** This approach has been recently introduced in the clinical practice. It involves the use of ultrasonic energy to cut and seal tissues. Large studies are needed to validate this technique.

Flexible endoscopic diverticulotomy was first reported in 1995.\textsuperscript{21,22} It can be performed under conscious sedation with no need for general anesthesia and neck extension. This approach is appealing in patients with comorbidities
that complicate general anesthesia and in patients with anatomical features that prevent good exposure.

The septum division can be achieved through four different techniques:

- Needle-knife incision
- Hook-knife incision
- APC
- Monopolar forceps

Repeat sessions are common to reduce the risk of perforation. Overall morbidity rate is 15% with no deaths reported in the literature. Complications include subcutaneous cervical emphysema, esophageal perforation, and bleeding.\(^9\) Short-term studies demonstrate recurrence rates ranging between 0% and 35%; long-term studies are needed to understand the role and outcomes of this approach.\(^9\)

To date, there are few studies (no randomized controlled trials) comparing open and endoscopic approaches. The results of these studies show that endoscopic surgery is associated with shorter operative time, lower morbidity, and shorter hospital stay than open surgery. Symptom relief rates are similar after both approaches.\(^9,15,23–25\) However, the heterogeneity of these studies in inclusion criteria, sample size, and length of follow-up do not allow for any definitive conclusions.

In summary, several options are available for the surgical treatment of Zenker diverticula. Because each treatment option has advantages and disadvantages, patient selection is key to achieving satisfactory short- and long-term outcomes. In the absence of a high level of evidence, there is no consensus regarding the best approach, and a “tailored” approach is advocated.

**Mid-Esophageal Diverticulum**

**PATHOPHYSIOLOGY**

Mid-esophageal diverticula are a rare entity. They are often associated with mediastinal granulomatous disease, and these may develop secondary to traction exerted by inflamed mediastinal lymph nodes or malignancy.
SYMPTOMS AND DIAGNOSIS

Mid-esophageal diverticula are often asymptomatic and incidentally diagnosed on a barium swallow or upper endoscopy. An esophageal manometry is usually obtained to assess the presence of an esophageal motility disorder, which is detected in about 90% of patients.\textsuperscript{2,26,27}

TREATMENT

While asymptomatic diverticula are not treated, symptomatic diverticula can be addressed with diverticulectomy or diverticulopexy. The decision for intervention is tempered by the underlying diagnosis that may take precedence. Diverticulectomy is the procedure of choice and it can be performed either by an open transthoracic approach or by thoracoscopy.\textsuperscript{26,28,29} Even though the concomitant presence of a motor disorder implies the necessity to perform a myotomy below the diverticulum, there is no consensus regarding the indication to add a myotomy to the diverticulectomy.\textsuperscript{30,31}

Epiphrenic Diverticulum

PATHOPHYSIOLOGY

Epiphrenic diverticulum of the esophagus is a rare entity. These are located in the distal 10 cm of the esophagus and in about 70% of cases arise on the right side of the esophagus (\textbf{Figs 21-2} and \textbf{21-3}). Even though most patients have a single epiphrenic diverticulum, two or more diverticula are found in about 15% of patients. A primary esophageal motility disorder, such as achalasia or diffuse esophageal spasm, is often present in patients with epiphrenic diverticulum and is thought to play a role in the development of the diverticulum and in the patient’s symptoms.\textsuperscript{32–38} The lack of coordination between the distal esophagus and the lower esophageal sphincter leads to increased endoluminal pressure with subsequent development of the diverticulum. Nutcracker esophagus and hypertensive lower esophageal sphincter are less frequently associated with epiphrenic diverticula. In some patients, the esophageal motility assessed by manometry is normal. This may be due to the intermittent nature of diffuse esophageal spasms for some
FIGURE 21-2  Barium swallow: epiphrenic diverticulum with a wide neck on the right side of esophagus a few centimeters above the gastroesophageal junction.
FIGURE 21-3 Barium swallow: large epiphrenic diverticulum located on the left side of the esophagus with a fluid-air level; dysmotility of the distal esophagus.

SYMPTOMS AND DIAGNOSIS

Most patients with epiphrenic diverticulum are symptomatic. The size of diverticulum does not correlate with the severity of symptoms, since the underlying esophageal motility disorder is the cause of complaints rather than the diverticulum per se. Dysphagia, regurgitation of undigested food, and chest pain are the most common symptoms. The Eckardt score is the most common clinical scoring system for achalasia. It is the sum of the scores for dysphagia, regurgitation, and chest pain (a score of 0 indicates the absence of symptoms, 1 indicates occasional symptoms, 2 indicates daily
symptoms, and 3 indicates symptoms at each meal) and weight loss (a score of 0 indicates no weight loss, 1 indicates a loss of less than 5 kg, 2 indicates a loss of 5-10 kg, and 3 indicates a loss of more than 10 kg). The maximum score on the Eckardt scale is 12.\textsuperscript{41}

Nocturnal cough, asthma, laryngitis, and recurrent pneumonia are secondary to aspiration of diverticular contents. Heartburn is less frequently reported, but may be due to stasis and fermentation of retained food in the distal esophagus.

The diagnostic workup includes

• Barium swallow
• Upper endoscopy
• Esophageal manometry

\textit{Barium swallow} is the most important diagnostic test since radiological findings are useful for the planning of the surgical treatment. This test provides information about size of the diverticulum, length and width of the neck of the diverticulum, and location and distance from the gastroesophageal junction. \textit{Upper endoscopy} should be routinely performed to rule out cancer of the distal esophagus as the cause of dysphagia, and any additional disease of the esophagus and the stomach. \textit{Esophageal manometry} is performed to detect the presence of any underlying esophageal motility disorder. However, it is argued it could be omitted since it does not affect the management strategies. In fact, motility disorders are found in almost all patients and a normal manometry does not exclude the presence of esophageal dysmotility, such as diffuse esophageal spasm which can be episodic in nature.

\textbf{TREATMENT}

The surgical treatment of epiphrenic diverticula consists of diverticulectomy, cardiomyotomy (to address the underlying esophageal motor disorder and to reduce the risk of staple line leak and recurrence of the diverticulum), and partial fundoplication (to prevent postoperative pathologic reflux). Even though some authors suggest treating asymptomatic patients in order to prevent the risk of aspiration, we believe that an operation should be performed only in symptomatic patients. The reasons for this policy are that
(1) symptoms will develop in less than 10% of asymptomatic patients and (2) surgery is burdened by significant morbidity and mortality even in referral centers.\textsuperscript{36,37}

The last two decades have witnessed a shift in the surgical approach to symptomatic patients. While in the past the operation was performed with an open left transthoracic approach, nowadays laparoscopy is considered the approach of choice, as (1) single-lung ventilation is avoided, with no need for a chest tube at the end of the procedure, (2) it provides a better exposure of the distal esophagus, (3) it allows the introduction of the stapler parallel to the esophagus, and (4) it allows the addition of a partial fundoplication.\textsuperscript{42} In addition, postoperative pain is reduced and the hospital stay is shorter after laparoscopic surgery. This operation brings relief of symptoms in 85% to 100% of patients.\textsuperscript{39}

However, laparoscopic epiphrenic diverticulectomy is a challenging procedure. Staple line leaks occur in up to 23% of cases, pulmonary complications are observed in 8% to 10% of patients, and mortality rates range between 0% and 7%.\textsuperscript{14} The main limitations of the laparoscopic approach are the distance of the diverticulum from the hiatus and the size of the diverticulum. The approximation of the muscular layers might be very challenging when the diverticulum is large and the diverticular neck is high in the mediastinum. In addition, a wide neck may require two or more cartridges of the stapler, thus creating a point of weakness where staple lines cross. Therefore, we suggest a tailored approach. When the upper pole of the diverticulum is too high to be safely dissected by laparoscopy or severe adhesions are present, the myotomy and the fundoplication can be completed laparoscopically, but the diverticulectomy may require a transthoracic approach.

Several factors, including distance of the diverticulum from the gastroesophageal junction, severe inflammation, and adhesions between the wall of the diverticulum and the pleura, might limit the feasibility of laparoscopic diverticulectomy.

We have recently reviewed our experience with 13 patients with symptomatic epiphrenic diverticulum who had undergone laparoscopic myotomy and partial anterior fundoplication.\textsuperscript{43} In six patients the diverticulum was resected, while in seven it was left in place. In three patients the epiphrenic diverticulum was left in place because it was small
(between 2 and 3 cm) and in four patients because the upper border of the diverticular neck and the upper pole could not be safely dissected laparoscopically secondary to a long distance from esophagogastric junction, or severe adhesions. Follow-up of these patients revealed that similar Eckardt scores were reported in both groups, confirming that a myotomy alone can provide relief of symptoms and suggesting that the underlying motility disorder rather than the diverticulum may be the cause of symptoms. We recommend a second procedure through the chest no earlier than 4 to 6 weeks after the first operation in patients in whom the diverticulum is not resected for technical reasons but who still experience symptoms. An expectant strategy should be followed if the patient experiences resolution of symptoms.

Technical Details. Five ports are placed as described during a Heller myotomy for achalasia. The operation starts with the opening of the gastrohepatic ligament all the way to the right pillar of the crus, which is separated from the esophagus. The peritoneum overlying the esophagus is then transected, and the esophagus is separated from the left pillar of the crus. All short gastric vessels are taken down to the left pillar of the crus. Both the anterior and the posterior vagus nerves are identified and preserved. A Penrose drain is passed around the esophagus, incorporating the nerves. The surgeon then proceeds with dissection of the esophagus in the posterior mediastinum in order to bring the diverticulum as close as possible to the hiatus. The neck of the diverticulum, the lower and the upper pole, and the lateral aspect of the pouch are freed from surrounding structures. After passing a 56-Fr bougie down the esophagus into the stomach, the neck of the epiphrenic diverticulum is transected by using a linear Endo-GIA stapler with 3.5-mm staples. The staple line is covered by approximating the muscle layers with interrupted 2-0 silk stitches. A myotomy is performed in the 1 o’clock position, extending all the way to the level of the upper extent of the diverticular neck and about 2 cm onto the gastric wall. Finally, a Dor fundoplication is constructed to prevent postoperative reflux.

In conclusion, laparoscopic diverticulectomy, cardiomyotomy, and partial fundoplication are the procedure of choice for the treatment of symptomatic epiphrenic diverticula in most cases. Small diverticula can be left in place and the treatment should be oriented to treat the underlying motility disorder by myotomy and fundoplication. Large diverticula with wide neck require a
ESOPHAGEAL BENIGN TUMORS AND CYSTS

Benign tumors arising from the esophageal wall and esophageal cysts are rare (1%-2% of resected esophageal lesions). Benign tumors can originate from each of the following layers of the esophageal wall: mucosa, submucosa, muscularis propria, and periesophageal tissues. They are classified according to the histologic tumor type and the location: intramural (leiomyoma [the most common], gastrointestinal stromal tumor [GIST], and schwannoma), and intraluminal (epithelial polyp, lipomatous polyp, fibrovascular polyp, papilloma, granular cell tumor, hemangioma). Most of these tumors are diagnosed between the third and fifth decade of life. Children are more likely to present with symptoms secondary to cysts or duplications, which are discussed below.

Benign Tumors

SYMPTOMS AND DIAGNOSIS

Benign tumors are asymptomatic and found incidentally in more than 50% of cases by upper endoscopy or other imaging tests obtained for other reasons. Presenting symptoms can be categorized as follows:

- Dysphagia secondary to obstruction by intraluminal tumor growth
- Pain and pyrosis
- Respiratory symptoms (more common in children) secondary to tracheal or bronchial compression
- Cardiac arrhythmia secondary to cardiac compression
- Ulceration and bleeding

The diagnosis of a benign tumor is frequently incidental. The evaluation of a patient with an esophageal benign tumor includes the following tests (Fig. 21-4):
**FIGURE 21-4** Esophageal leiomyoma. Barium swallow (A), endoscopy (B), and endoscopic ultrasound (C) show the presence of a mass arising from the submucosa of the esophagus that narrows the esophageal lumen.

- **Upper endoscopy** rules out the presence of cancer or other esophageal diseases and allows for biopsy of mucosal lesions. In addition, this test confirms the intact mucosa in the case of suspected submucosal tumors.
- **Barium swallow** helps to assess the location of the mass and identify other esophageal pathology.
- **Endoscopic ultrasound** provides information about (1) the layers of the esophageal wall that are involved by the mass, (2) the sonographic features of the mass that are often diagnostic, and (3) the size of periesophageal lymph nodes. In addition, needle biopsies of submucosal lesions can be taken under ultrasonic guidance with higher accuracy than endoscopic biopsy.
- **Chest computed tomography (CT)** helps define the relationships between the esophageal mass and periesophageal tissues and mediastinal organs.

**TREATMENT**

Resection of the benign esophageal tumor is indicated in symptomatic patients and in the presence of masses suspicious for malignancy or with potential risk of malignant evolution (adenoma and gastrointestinal stroma tumors). The excision can be accomplished by an endoscopic or surgical approach. The main indication for resection by endoscopic mucosal resection and endoscopic submucosal dissection are intraluminal lesions smaller than 2 cm and originating from mucosa or submucosa. Most other lesions are now removed by minimally invasive resections (thoracoscopic or laparoscopic)
that are associated with low complication rates, excellent postoperative recovery, and low mortality rates.\textsuperscript{49–52} Surgical enucleation is the most common procedure and is performed by laparoscopy or thoracoscopéy according to the location of the mass.\textsuperscript{48} Briefly, the surgeon first performs a longitudinal myotomy incising and splitting the muscular fibers, then bluntly dissects the tumor from the muscular layer and the submucosa, leaving the mucosa intact. The presence of mucosal injuries should be always checked with intraoperative endoscopy and air insufflation. Finally, the surgeon reapproximates the muscular edges to minimize the risk of diverticulum formation.

Esophagectomy is required in about 10\% of patients, mainly those with leiomyomas larger than 8 cm involving the esophagus circumferentially, or with suspicion for leiomyosarcoma, and in patients with a GIST larger than 5 cm or other features of malignancy.\textsuperscript{48}

**Cysts and Duplications**

This group of esophageal diseases includes (1) congenital malformations that originate from aberrations of the development of esophagus or trachea and (2) inclusion and neuroenteric cysts. While esophageal cysts have muscular and epithelial layers and bronchogenic cysts include cartilage, inclusion cysts have an epithelial lining with no muscle or cartilage. Neuroenteric cysts are secondary to aberrant separation of the esophagus from the spinal column and are located on the posterior aspect of the esophagus.\textsuperscript{53} These manifest with dysphagia, infection, or hemorrhage.

Diagnosis of an esophageal cyst is performed by upper endoscopy, barium esophagram, endoscopic ultrasound, CT scan, and magnetic resonance imaging (Fig. 21-5). Since the fluid-filled nature of the lesion is pathognomonic in most cases, biopsies are usually not necessary. Following identification, these malformations are resected through a thoracoscopic approach under endoscopic guidance. Both symptomatic and asymptomatic lesions are resected due to the risk of infection, mucosal erosion, and fistulization.\textsuperscript{54} Cyst removal can be achieved by enucleation or esophageal resection in cases where the cyst is intramural and fused to the esophageal wall.\textsuperscript{55} Previous biopsies and cyst infections might make the resection more challenging due to adhesion formation, and an open transthoracic approach
may be required.55

FIGURE 21-5 Esophageal cyst. Barium swallow (A), endoscopy (B), and endoscopic ultrasound (C) demonstrate the presence of a fluid-filled cyst arising from the wall of the distal esophagus.

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2094.


ACHALASIA AND OTHER MOTILITY DISORDERS

Jeffrey A. Blatnik • Jeffrey L. Ponsky

INTRODUCTION

Esophageal motility is a complex and multifactorial process that functions to pass food and liquid through the esophagus. Using systematic contractions in the esophageal body, combined with an appropriately timed relaxation of the lower esophageal sphincter (LES), the bolus is able to pass from the esophagus into the stomach. Errors in the process can occur anywhere along this chain of events and can lead to significant morbidity for patients. The constellation of presenting symptoms includes dysphagia, chest pain, and reflux. Due to these often vague symptoms, many patients undergo multiple other therapies prior to being diagnosed with an esophageal motility disorder and ultimately go on to further treatment. It is reasonable to start with a short course of acid suppression therapy in patients; however, when their symptoms fail to improve, this should prompt additional workup.

Achalasia is by far the most commonly diagnosed disease of esophageal motility; however, numerous other dysmotility patterns exist. The advent of high-resolution manometry has led to new understanding of esophageal
function. In addition, the information obtained from advanced diagnostics has led to improved patient selection for the various management options available. This chapter will review the common esophageal motility disorders, their diagnosis, and their management.

NORMAL ESOPHAGEAL FUNCTION

A normal esophagus varies from 18 to 25 cm in length and serves to transport food from the oropharynx to the stomach. Structurally, the esophagus is made up of 4 primary layers, including the innermost mucosa, submucosa, muscularis propria, and adventitia. The muscle layer includes the innermost circular fibers and the outer longitudinal fibers, of which the upper third consists mostly of striated muscle, whereas the lower two-thirds are primarily smooth muscle. In addition to the circular and longitudinal muscles, the esophagus also contains 2 muscular sphincters. The upper esophageal sphincter controls the entrance of food to the esophagus from the oropharynx, whereas the LES prevents reflux of acid contents into the esophagus from the stomach.

Normal esophageal function is a complicated and well-choreographed event. When food is swallowed, the epiglottis moves backward to prevent aspiration and to direct food into the esophagus all while the upper esophageal sphincter relaxes. Primary peristalsis transfers the bolus down the esophagus by rhythmic contractions, which are controlled by excitatory activity in the vagal nucleus ambiguous, which releases acetylcholine. In coordination and prior to the excitatory signal, inhibitory neurons (which release nitric oxide and vasoactive intestinal peptide) are activated by the preganglionic neurons and provide deglutitive inhibition. As one moves further down the esophagus toward the stomach, there is an increased inhibitory action called the latency gradient. This delays contractions and allows the bolus to move forward toward the stomach. In contrast to primary peristalsis, secondary peristalsis is elicited by esophageal distension and is a local reflex that independently causes contraction of the esophagus. It is the relationship of inhibitory and excitatory signals along the esophagus that provides the coordinated forward movement of the food bolus. A disruption of this balance is thought to lead to esophageal motility disorders such as achalasia.
DIFFERENT TYPES OF ESOPHAGEAL DISORDERS

Esophageal motility disorders make up a broad spectrum of diseases with varied presentations and symptoms. Initial differentiation divides them into primary motility disorders versus secondary motility disorders that are manifestations of systemic diseases. By far, the most well-described primary motility disorder is achalasia, which results from failure of the LES to relax and causes varied esophageal contractions. Other primary motility disorders to be discussed in this chapter include diffuse esophageal spasm and nutcracker esophagus.

ACHALASIA

Epidemiology

Achalasia is the most well-studied esophageal motility disorder, with an estimated incidence of 1 per 100,000 worldwide. However, achalasia is a chronic disease, and as a result, the prevalence is estimated to be between 9 and 10 per 100,000 people. Sex and race do not appear to have a significant impact on the incidence of achalasia. However, there is increasing evidence supporting a genetic role. This finding comes from twin and sibling studies and from association of achalasia with other diseases such as Parkinson disease and Down syndrome. However, genetic testing in achalasia is limited primarily to research studies with limited diagnostic utility.

Pathophysiology

The cause of achalasia is felt to be the functional loss of myenteric plexus ganglion cells of the distal esophageal sphincter and lower esophagus. This leads to a loss of inhibitory signals and eventually unopposed excitatory signals and the inability of the LES to relax. Although a definitive cause is unknown, most researchers feel that it is an autoimmune process that leads to loss of the myenteric plexus. This is supported by histologic exam in which the ganglion cells that do remain are often surrounded by lymphocytes and
In addition, some patients with achalasia also experience dysfunction of the upper esophageal sphincter, leading to difficulty with belching. In unaffected patients, when gas from the stomach enters the esophagus, it triggers a relaxation of the upper esophageal sphincter. However, in some patients with achalasia, this reflex is lost presumably due to the loss of inhibitory neurons. This may also be a contributing factor to esophageal distension seen in patients with chronic achalasia. Finally, although rarely seen in Western countries, Chagas disease is a well-known cause of achalasia. Secondary to an infection with the parasite *Trypanosoma cruzi*, Chagas disease leads to widespread myenteric plexus destruction and subsequently achalasia.

**Signs and Symptoms**

For most patients, achalasia has an insidious onset with gradual progression of symptoms. Most commonly, this includes dysphagia that progresses from solids to liquids, and patients can often go years before seeking appropriate medical attention. Patients frequently undergo therapy for other diseases such as gastroesophageal reflux disease before being diagnosed with achalasia.

The most common symptoms associated with achalasia include dysphagia to solids (91%) and liquids (85%) and regurgitation of food and saliva (45%-75%; Table 22-1). Although dysphagia is seen in nearly all patients with achalasia, it can also be observed in up to 4% of adults in the United States. After dysphagia, additional nonspecific symptoms include chest pain, epigastric pain, weight loss, and odynophagia. Although not clearly diagnostic of achalasia, these symptoms are often part of the clinical picture.

**TABLE 22-1: RATES OF SYMPTOM PRESENTATION IN PATIENTS WITH ACHALASIA**
Respiratory symptoms are also occasionally seen in patients with achalasia and are thought to be related to chronic aspiration due to failed clearance of food and liquid from the esophagus. Symptoms including sore throat, hoarseness, or postnasal drip are seen in up to 71% of patients, and cough is seen in 61% of patients. However, most patients who report respiratory symptoms often have had symptoms of dysphagia for 2 or more years prior to the onset of their respiratory symptoms.

Finally, patient demographics may alter patient symptoms at presentation. Younger patients often present with symptoms of chest pain and heartburn more frequently than older patients. In addition, older patients tend to be overall less symptomatic than their younger counterparts. Finally, obese patients with a body mass index $\geq 30 \text{ kg/m}^2$ often experience symptoms of choking and vomiting more frequently before myotomy compared with nonobese patients.

### Diagnosis and Workup

Patients who initially present with complaints of dysphagia are often initially trialed on a course of a proton pump inhibitor (PPI). Although this is appropriate, when symptoms fail to improve after a 4 to 6 weeks, further evaluation is warranted. For most patients, the appropriate next step would be to proceed with an upper endoscopy with mucosal biopsy. This is crucial to rule out any underlying inflammatory ring, erosive gastroesophageal reflux, eosinophilic esophagitis, and esophageal cancer. The entity of an esophageal structural abnormality leading to achalasia symptoms is termed *pseudoachalasia*. Other endoscopic findings often seen in patients with

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rate (%)</th>
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<tbody>
<tr>
<td>Dysphagia for solids</td>
<td>90</td>
</tr>
<tr>
<td>Dysphagia for liquids</td>
<td>85</td>
</tr>
<tr>
<td>Heartburn/reflux</td>
<td>75</td>
</tr>
<tr>
<td>Regurgitation or vomiting</td>
<td>45</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>15</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>5</td>
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</tbody>
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achalasia include a dilated and tortuous esophagus, residual food and fluid in the esophagus, and difficulty passing food and fluid through the LES (Fig. 22-1). Finally, patients with achalasia often develop *Candida* esophagitis secondary to the stasis.
Although endoscopic findings can be suggestive of achalasia, additional evaluation with barium esophagram is recommended. This can provide details on both anatomy and function of the esophagus. A classic “bird beak” presentation (Fig. 22-2) can often be seen in patients with achalasia; other findings on esophagram include a dilated esophagus with aperistalsis and a corkscrew appearance in more severe cases. Similar to endoscopy, although these findings are suggestive of achalasia, they are insufficient for a definitive diagnosis. The next step in evaluation should include esophageal manometry.
Traditional manometry, which includes water-perfused and strain gauge systems, has been for the most part replaced with more modern, reproducible,\textsuperscript{24} and accurate\textsuperscript{25} high-resolution manometry (HRM) catheters.
Specifically, HRM catheters have sensors spaced every 1 cm along the length of the catheter, in contrast to every 3 to 5 cm seen in traditional manometry. The result of the study is an esophageal pressure topography, which reports the pressure in a color scale compared with time and location within the esophagus (Fig. 22-3). These catheters are placed either directly or under endoscopic guidance (Fig. 22-4) through the LES and into the stomach to facilitate measuring the pressure of the distal esophagus and LES.

Manometric findings consistent with achalasia include incomplete relaxation of the LES, which distinguishes it from other disorders associated with aperistalsis. In normal individuals, there is complete relaxation of the LES during a swallow (to a measured level <8 mm Hg above gastric pressure). However, in patients with achalasia, the LES relaxation during swallow may be incomplete or absent all together. Additional manometric findings consistent with achalasia include an elevated resting LES pressure of >45 mm Hg and aperistalsis in the distal two-thirds of the esophagus.26
FIGURE 22-3  Sample normal high-resolution manometry. Vertical axis represents distance in centimeters, and horizontal axis represents time in seconds. The colors represented in the figure indicate the pressure, with blue being 0 and purple being the highest pressure. You can see the peristaltic contraction, the upper esophageal sphincter (UES), and the esophagogastric junction (EGJ).

FIGURE 22-4  High-resolution manometry probe placed at the time of endoscopy. High-resolution manometry is critical for differentiating symptoms of dysphagia or chest pain in patients.

More widespread use and investigation of HRM have led to the ability to subtype achalasia based on the patterns of esophageal pressurization and the creation of a new classification scheme for motility disorders called the Chicago Classification.\(^{27}\) The ability to subtype patients with achalasia has enabled the development of clinically relevant phenotypes.\(^{28}\)

- Type I (classic) achalasia: Impaired LES relaxation, absent peristalsis, and normal esophageal pressure
• Type II achalasia: Impaired LES relaxation, absent peristalsis, and increased panesophageal pressure
• Type III (spastic) achalasia: Impaired LES relaxation, absent peristalsis, and distal esophageal spastic contractions

When evaluating the different subtypes, it has been found that type II patients were significantly more likely to respond to any therapy (Botox, 71%; pneumatic dilation, 91%; or Heller myotomy, 100%) than type I (56% overall) or type III patients (29% overall).\textsuperscript{28} This information has improved our ability to discuss expected outcomes with our patients.

In cases without a clear diagnosis after endoscopy, barium esophagram, and manometry, there may be benefit from additional evaluation of the LES by endoscopic ultrasound\textsuperscript{29} or timed barium esophagram to document contrast bolus retention.

**Treatment**

There is no cure for achalasia; rather, treatment is aimed at palliating the symptoms that patients experience. Therapies are directed at reducing the contractility in the LES, thus allowing for adequate esophageal emptying. Overall, the goal is early diagnosis and therapy to prevent late complications while preserving esophageal function.

**MEDICAL**

Medical therapy is the least invasive but also least effective treatment option for patients with achalasia, and as such, it is reserved for patients who cannot tolerate other treatments. Although initial response to medical therapy is approximately 50%, long-term success is limited by side effects, which include headache, orthostatic hypotension, and edema. The primary medical therapy for achalasia includes oral calcium channel blockers or nitrates, which can result in relaxation of the LES pressure in up to 47% to 64% of patients.\textsuperscript{30} Nifedipine (10-30 mg administered 30-45 minutes before meals) and isosorbide dinitrate (5-10 mg administered 10-15 minutes before meals) are the 2 most widely used medical therapies; however, some studies suggest that isosorbide dinitrate may provide a more rapid response.\textsuperscript{31}
Finally, phosphodiesterase-5 inhibitors, such as sildenafil, have also been used to treat patients with achalasia. They have been found to inhibit the contractile activity of the esophageal musculature in patients with achalasia, resulting in decreased LES tone. Although initial studies have suggested some symptom improvement, long-term results are lacking.

**BOTULINUM TOXIN**

Botulinum toxin therapy is considered for patients who are not good candidates for more definitive therapy such as pneumatic dilation or surgical or endoscopic myotomy. Under endoscopic guidance, botulinum toxin is injected into the LES and ultimately blocks the excitatory (acetylcholine-releasing) neurons that lead to the increase in the LES smooth muscle. The overall effect is a decrease in the resting pressure of the LES, allowing the esophagus to empty into the stomach. Initial symptom improvement rates of botulinum toxin are similar to those of pneumatic dilation and approach 70%. However, patients tend to have more frequent recurrence of symptoms in as little as 6 months. Finally, it has been found that repeated botulinum toxin injection may make subsequent myotomy more difficult and possibly result in worse outcomes compared to patients who undergo myotomy alone.

**PNEUMATIC DILATION**

Pneumatic dilation involves using a noncompliant cylindrical balloon to dilate the LES, essentially tearing its muscle fibers. The dilation should only be performed by an experienced endoscopist and is done under endoscopic and fluoroscopic guidance. Prior to proceeding with endoscopic dilation, patients should be considered appropriate surgical candidates due to the potential for esophageal rupture during dilation. Numerous studies have been done evaluating the efficacy of pneumatic dilation (Table 22-2), with short-term success rates ranging from 60% to 90% and results generally sustained for up to 2 years. However, the number of patients who continue to have symptom relief wanes over time. In addition, nearly one-third of patients will go on to require additional therapy after pneumatic dilation. Despite this, pneumatic dilation is considered the most cost-effective treatment for achalasia and has the advantage of being less invasive than some surgical
The greatest risk associated with pneumatic dilation is esophageal perforation after the procedure. This can range from small, clinically insignificant perforations managed with antibiotics, total parenteral nutrition, or esophageal stent placement to major disruptions requiring emergent surgical exploration and repair. The rate of esophageal perforation following pneumatic dilation ranges in the literature from 0% to 15%\textsuperscript{41,42}; however, recent studies at high-volume centers place the rate at approximately 1% to 5%.\textsuperscript{36,43} There are no predilation factors that have been found to be associated with a risk of perforation, but it is most likely due to an inappropriately positioned balloon. As a result of this risk, it is recommended that surgical backup be readily available when performing pneumatic dilation. The most commonly seen complication following pneumatic dilation is gastroesophageal reflux disease, with rates approaching 20%.\textsuperscript{44} Symptomatic patients are often able to be successfully treated with PPI therapy.

Commercially available balloons come in 3 sizes (3.0, 3.5, and 4.0 cm in diameter); in comparison, the largest through-the-scope balloon is typically 2.0 cm. It is recommended to start with a 3.0-cm balloon that is confirmed to be in position across the LES by fluoroscopy or endoscopy. It is then insufflated with a hand-held pressure gauge for 15 to 60 seconds. After

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**TABLE 22-2: RANDOMIZED CONTROLLED TRIALS OF PNEUMATIC DILATION VERSUS LAPAROSCOPIC HELLER MYOTOMY (LHM) FOR THE TREATMENT OF ACHALASIA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Comparison</th>
<th>Sample Size</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persson et al\textsuperscript{37}</td>
<td>2015</td>
<td>Pneumatic dilation vs LHM with posterior fundoplication</td>
<td>53</td>
<td>3-year treatment failure: 32% for pneumatic dilation vs 4% for LHM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-year treatment failure: 36% for pneumatic dilation vs 8% for LHM</td>
</tr>
<tr>
<td>Boecksxtaens et al\textsuperscript{36}</td>
<td>2011</td>
<td>Pneumatic dilation vs LHM and Dor fundoplication</td>
<td>201</td>
<td>Eckardt score ≤3 at 12 months: 90% for pneumatic dilation vs 93% for LHM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eckardt score ≤3 at 24 months: 86% for pneumatic dilation vs 90% for LHM</td>
</tr>
<tr>
<td>Novais et al\textsuperscript{72}</td>
<td>2010</td>
<td>Pneumatic dilation vs LHM</td>
<td>94</td>
<td>3-month clinical response: 73.1% for pneumatic dilation vs 88.3% for LHM</td>
</tr>
<tr>
<td>Kostic et al\textsuperscript{73}</td>
<td>2007</td>
<td>Pneumatic dilation vs LHM with Toupet fundoplication</td>
<td>51</td>
<td>12-month treatment failure: 23% for pneumatic dilation vs 4% for LHM</td>
</tr>
</tbody>
</table>
dilation, all patients must undergo radiographic evaluation with a gastrograffin study, followed by barium esophagram to evaluate for esophageal perforation. If patients fail to improve symptomatically, additional dilations can be performed with progressively larger balloons in 4 to 6 weeks. Long-term symptom improvement also appears to be improved with serial dilation compared with single pneumatic dilation. Success following pneumatic dilation appears to be impacted by patient characteristics such as age (improved outcomes if >45 years), sex (improved outcomes in females), esophageal diameter, and achalasia subtype.

**SURGICAL APPROACH**

The original surgical approach to achalasia involved division of the circular and longitudinal esophageal muscle fibers through a thoracotomy with overall good results. However, this approach has been replaced by a minimally invasive, laparoscopic, transabdominal approach (Heller myotomy) with or without a fundoplication due to lower perioperative morbidity and faster recovery compared with thoracotomy. Heller myotomy offers superior results when compared with single pneumatic dilation, with efficacy rates ranging from 88% to 95%. However, this superiority is less evident when compared with serial and graded pneumatic dilation. In addition, similar to pneumatic dilation, the efficacy of Heller myotomy can decrease over time, with symptom improvement decreasing from nearly 96% at 6 months to 57% to 92% at 6 years.

Gastroesophageal reflux disease after surgical myotomy continues to be a frequent problem, with rates approaching 30%. The addition of a surgical fundoplication has been found in a blinded, randomized controlled trial to reduce the rate of abnormal acid exposure in the esophagus from 47% to 9%. As such, the Society of American Gastrointestinal and Endoscopic Surgeons currently recommends that a fundoplication be included following surgical myotomy to prevent reflux. However, the preferred approach to fundoplication (anterior Dor vs posterior Toupet) remains uncertain.

The procedure begins with a standard 4- to 5-port laparoscopic approach. After dividing the gastroesophageal ligament, the esophageal fibers are identified. Both the outer longitudinal and inner circular fibers are then divided either with blunt traction or the use of electrocautery for a distance of
4 to 6 cm proximal along the esophagus from the gastroesophageal junction and 2 cm distal onto the body of the stomach (Fig. 22-5). Following division of the muscle fibers, the fundoplication is then performed.

**FIGURE 22-5** Completed laparoscopic Heller myotomy prior to any fundoplication. The *arrows* point to the divided esophageal and gastric muscle, demonstrating a bulging mucosa between them. This step is then usually followed by either a Dor or Toupet fundoplication.

**PNEUMATIC DILATION VERSUS SURGICAL MYOTOMY**

Initial studies comparing pneumatic dilation and surgical myotomy (Table 22-2) demonstrated that surgical myotomy was associated with improved long-term symptom improvement when compared with pneumatic dilation (68.2% vs 56.3%). However, patients underwent only single pneumatic dilation, which is not the current recommendation. In one of the most referenced prospective, randomized trials comparing surgical myotomy and graded pneumatic dilation, no significant difference in success rates after 2 years of follow-up was found (92% for pneumatic dilation vs 87% for surgical myotomy). Thus, it appears that laparoscopic surgical myotomy
and pneumatic dilation have comparable success rates.

**PERORAL ENDOSCOPIC MYOTOMY**

Probably the most recent advancement in the management of achalasia comes in the form of peroral endoscopic myotomy (POEM). First described in 2010 by Inoue et al, this procedure involves using a standard flexible gastroscope with a transparent cap to make a small cut in the esophageal mucosa approximately 14 cm proximal to the gastroesophageal junction. This is then used to enter into the submucosal plane and create a tunnel along the length of the esophagus and onto the body of the stomach. Following creation of the tunnel, it is then used to access and divide the esophageal muscle fibers using electrocautery. The final step involves closing the mucosal opening either with endoscopic clips or sutures (Fig. 22-6).
FIGURE 22-6 The 4 key steps in performing a peroral endoscopic myotomy (POEM). A. After performing a submucosal injection, a mucosotomy is performed to gain access to the submucosal space. B. The submucosal tunnel is continued down the length of the esophagus and onto the stomach using intermittent injections of methylene blue solution and electrocautery. C. Following creation of the submucosal tunnel, the myotomy is performed. There are numerous variations on this approach; however, the ultimate goal is to divide at minimum the circular fibers on the esophagus and onto the stomach. D. Following completed myotomy, the mucosotomy created at the
beginning is then closed with either clips or endoscopic sutures.

Although long-term studies are lacking, many series report success rates of over 90% at 1 year follow-up. A recent meta-analysis comparing POEM with surgical myotomy demonstrated equivalent short-term outcomes between the 2 treatments with comparable rates of complications. POEM is gaining increased exposure for the treatment of achalasia, but more long-term studies are needed. Similar to surgical myotomy, gastroesophageal reflux disease remains a common complication following POEM and is reported in 10% to 46% of patients. For this reason, most patients are placed on PPI therapy after POEM until subsequent pH testing can be completed.

**Follow-Up and Treatment Failures**

The rate of esophageal squamous cell carcinoma is increased in patients with achalasia compared to the general population (hazard ratio of developing cancer, 28). There is also some concern for increased risk of adenocarcinoma; however, this risk is significantly lower than that for squamous cell carcinoma. The mechanism for increased malignancy is thought to be secondary to stasis within the esophagus and increased inflammation. Regardless, the risk is still low overall, and there are insufficient data to support routine endoscopic surveillance for patients with achalasia.

The current management of achalasia is aimed at alleviating symptoms, but some patients go on to develop megaesophagus or “end-stage” achalasia. These patients present with a markedly dilated and tortuous esophagus. As such, pneumatic dilation is often unsuccessful, and patients require surgical myotomy or POEM with improvement in symptoms. However, some patients may ultimately require esophagectomy typically with gastric pull up for management of symptoms. Uncontrolled studies report that 80% of patients have improvement of their symptoms following esophagectomy, with mortality rates ranging from 0% to 5.4%.

**DIFFUSE ESOPHAGEAL SPASM**

Diffuse esophageal spasm (DES) is characterized by uncoordinated and
simultaneous contractions of normal amplitude within the distal esophagus. The contractions do not propel food effectively to the stomach, and patients tend to present with symptoms of dysphagia, regurgitation, and chest pain. On HRM, DES is characterized by ≥20% premature contractions within the esophagus (Fig. 22-7). In contrast to achalasia, DES symptoms are intermittent, and findings on HRM may not be present on every series of test swallows. In addition, unlike achalasia patients, DES patients usually have normal relaxation of the LES. Contrast esophagram may show a corkscrew esophagus or rosary bead esophagus (Fig. 22-8).

**FIGURE 22-7** Sample high-resolution manometry for a patient with diffuse esophageal spasm. The patient has evidence of a high-amplitude contraction occurring simultaneously. UES, upper esophageal sphincter.
The pathophysiology of DES remains unknown but is thought to be associated with impairment of inhibitory innervation. An additional hypothesis is thought to be a dysfunction of endogenous nitric oxide synthesis within the esophagus. In one study reviewing patients presenting for evaluation of noncardiac chest pain and undergoing esophageal manometry, the prevalence of DES was 4%.\textsuperscript{62}

In patients diagnosed with DES, treatment is again focused on relieving symptoms. However, due to the intermittent nature of symptoms, no clear consensus exists on treatment algorithms. Medical management of DES is often focused on the primary symptom. In patients who present with dysphagia, therapy with a calcium channel blocker (diltiazem 60-90 mg 4 times a day) was found to reduce symptoms in select individuals.\textsuperscript{63} For patients whose primary symptom is chest pain, calcium channel blockers and
tricyclic antidepressants (imipramine 50 mg/d) have been shown to be effective in small trials.\textsuperscript{64} The use of pneumatic dilation for DES is not currently recommended due to the broad area affected. One small study evaluating the role of botulinum toxin injection for patients with DES found that the injection of botulinum toxin in 4 quadrants at 2 and 7 cm above the gastroesophageal junction improved total symptom scores.\textsuperscript{65} The use of surgical myotomy has been evaluated for patients who are refractory to medical therapy with varied success rates.\textsuperscript{66} Most recently, POEM has been evaluated for patients with DES. Using HRM to localize the extent of disease, POEM can be targeted to the affected area. In a small study of 5 patients who underwent POEM for DES, the overall rate of symptom relief was 71%.\textsuperscript{67}

**NUTCRACKER ESOPHAGUS**

In contrast to DES and achalasia, nutcracker esophagus (hypertensive peristalsis) is characterized by normal sequential esophageal contractions; however, they are of extreme amplitude or duration. Nutcracker esophagus on conventional manometry is defined as high-amplitude peristaltic contractions of >180 to 220 mm Hg in the distal esophagus. On HRM, the high-pressure contractions are measured as the distal contractile integral (DCI), with $\geq$20% of DCI measuring $>8000$ mm Hg·s·cm (Fig. 22-9).\textsuperscript{27} In addition, many patients with nutcracker esophagus may also have a hypertensive or poorly relaxing LES, which can lead to some overlap in the diagnosis. Contrast esophagram in patients with nutcracker esophagus often shows a rosary bead pattern (Fig. 22-10).
FIGURE 22-9 Sample high-resolution manometry in a patient with nutcracker esophagus. It demonstrates preserved peristaltic activity, but with significantly elevated amplitude. This is typically >180 mm Hg of pressure. UES, upper esophageal sphincter.
FIGURE 22-10 Barium esophagram of a patient with nutcracker esophagus demonstrating a rosary bead pattern. This is similar in appearance to a patient with diffuse esophageal spasm (DES) and requires the addition of high-resolution manometry to differentiate.

Patients with nutcracker esophagus tend to present more frequently with symptoms of chest pain rather than dysphagia due to the coordinated nature of the contractions. In addition, patient symptoms often do not correlate with the results of manometric studies. In one study evaluating 910 patients
referred for noncardiac chest pain, 12% were found to have manometry tracings consistent with nutcracker esophagus.\textsuperscript{68}

Therapy for patients with nutcracker esophagus is similar to DES. One small randomized trial of 22 patients with nutcracker esophagus found that a calcium channel blocker (diltiazem 60-90 mg 4 times a day) significantly relieved chest pain when compared with placebo.\textsuperscript{69} Also similar to DES, tricyclic antidepressants have shown limited success in alleviating symptoms.\textsuperscript{64,70} Surgical myotomy has shown some success in relieving dysphagia symptoms; however, improvements in chest pain are less consistent.\textsuperscript{71} The use of POEM has also found some initial success in patients with nutcracker esophagus, but ongoing investigation is still required before widespread acceptance.\textsuperscript{67}

**CONCLUSION**

In conclusion, esophageal motility disorders present with a complicated disease pattern that relies on a high index of suspicion. Patients often present with symptoms of dysphagia or chest pain and undergo other therapies prior to being diagnosed with achalasia or other motility disorders. POEM marks a new treatment option that is finding increasing applications for esophageal motility diseases. Further studies are needed to determine what the long-term outcomes will be for patients undergoing POEM.

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GASTROESOPHAGEAL REFLUX DISEASE, HIATAL HERNIA, AND BARRETT ESOPHAGUS

Robert D. Bennett • David M. Straughan • Vic Velanovich

GASTROESOPHAGEAL REFLUX DISEASE OVERVIEW

Definition

Gastroesophageal reflux disease (GERD) is a chronic disorder involving pathologic retrograde flow of gastric contents into the esophagus. In 2006, an international group of 44 experts known as the Montreal Consensus defined GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.”¹ This definition was chosen to allow for patients to be diagnosed independent of the technology used during evaluation. Nonerosive reflux disease (NERD) is defined as
classic GERD symptoms in the absence of mucosal complications, and may\textsuperscript{2–4} account for 30\% to 70\% of patients presenting for endoscopy with reflux symptoms.

**Epidemiology**

Until 2006, when the definition of GERD became more standardized, varying frequency rates were reported. A systematic review performed in 2005 identified a prevalence rate between 10\% and 20\% in Europe and the United States, and less than 5\% in Asia.\textsuperscript{5} These findings of regional variation were updated and confirmed in 2014 by the same group. Occurrence of at least once-weekly episodes of heartburn or regurgitation or a diagnosis of GERD as defined by the Montreal Consensus or a physician was found to be 18.1\% to 27.8\% in North America, 23.0\% in South America, 8.8\% to 25.9\% in Europe, and 8.7\% to 33.1\% in the Middle East. In East Asian studies, prevalence of GERD ranges from 2.5\% to 7.8\% and 11.6\% in Australia.\textsuperscript{6}

Studies between 1992 and 2011 suggest that the prevalence of GERD may be increasing worldwide, but remains lowest in East Asia and highest in Western countries.\textsuperscript{5}

**Risk Factors and Associated Conditions**

Risk factors for the development of GERD include obesity, increasing age, and genetics (concordance rates are higher in monozygotic vs dizygotic twins). Behavioral factors may include alcohol consumption, tobacco use, and diet.\textsuperscript{5}

The prevalence of GERD does not increase with age, but symptom intensity may decrease after age 50.\textsuperscript{7} Prevalence of erosive esophagitis, however, does increase with age over 50.\textsuperscript{8}

GERD is frequently associated with pregnancy, often presenting as heartburn. While onset can occur at any point during a pregnancy, the majority of cases begin in the first trimester (52\%), with decreasing frequency of onset later in pregnancy (40\% in the second trimester, 8\% in the third trimester).\textsuperscript{9} Overall prevalence of symptoms, however, increases throughout pregnancy, with up to 72\% of pregnant patients reporting heartburn symptoms in the third trimester. Symptom severity also increases
as pregnancy progresses.\textsuperscript{10}

**PATHOPHYSIOLOGY**

**Normal Lower Esophageal Sphincter Anatomy/Physiology**

The lower esophageal sphincter (LES) is a physiologic high-pressure zone located just cephalad to the gastroesophageal junction (GEJ), which serves to prevent retrograde passage of gastric contents into the esophagus. The antireflux mechanism is supported by the lower esophageal musculature, interaction with the diaphragmatic hiatus, and maintenance of an intra-abdominal esophagus by the phrenoesophageal ligament. Any acid reflux that occurs is mitigated by neutralization of the gastric acid with alkaline saliva and minimization of contact of the acid with the esophageal mucosa by reflex clearing esophageal peristalsis.

The LES can be defined anatomically or physiologically. Anatomically, although difficult to identify clinically, the LES is composed of intrinsic and extrinsic contractile elements. The intrinsic contractile element is made up of circular, tonically contracted “clasp” muscle fibers within the distal esophagus, and diagonally oriented “sling” muscle fibers at the cardia-fundus junction (Fig. 23-1A). The extrinsic component is made up of crural fibers at the esophageal hiatus of the diaphragm, referred to as the diaphragmatic “pinch-cock” mechanism. Similar to the intrinsic component, these muscle fibers are in a state of tonic contraction, which contributes to the elevated resting pressure of the LES.\textsuperscript{11} During inspiration, these crural fibers further contract, contributing to measured pressure at the LES. Lastly, the increased pressure of the abdominal cavity relative to the thoracic cavity also exerts increased transmural pressure on the intra-abdominal portion of the LES. Physiologically, the LES represents a region of relatively high pressure when compared to the esophageal body. Normally, the LES spans the esophageal hiatus, with half of the functional high-pressure zone present above the diaphragm in the thorax, and half below the diaphragm in the abdomen. It is normally fixed in this position by the phrenoesophageal ligament, which originates from the transversalis fascia of the diaphragm and has two leafs
(Fig. 23-1B). The thin lower leaf attaches to the esophageal wall at the angle of His and a thicker upper leaf arises from the diaphragmatic fascia and attaches to the esophagus with collagenous extension.\textsuperscript{11} Innervation to the intrinsic musculature of the distal esophagus contributing to the LES is primarily vagal in nature, with parallel excitatory and inhibitory pathways which lead to contraction and relaxation, respectively.\textsuperscript{12}
FIGURE 23-1 Anatomy of the gastroesophageal junction. A. The clasp and sling muscle fibers that make up the lower esophageal reflux barrier in the contracted and relaxed state, respectively. B. The anatomic relationship of the

The esophagus is classically described as being 10 inches, or 25 cm, in length. Normal lower esophageal sphincter length is 2 to 4 cm, and the ratio of intra-abdominal to intrathoracic LES length (another way of expressing intra-abdominal length) is 1 to 1.2. In healthy volunteers, normal resting LES pressure is approximately 20 mm Hg (15-29 mm Hg), and is dependent on whether the measurements are taken at end-inspiration, mid-expiration, or end-expiration. The lower esophageal sphincter is maintained in a tonically contracted state by vagal innervations. LES pressure vectors are asymmetrical, with higher pressures anterior and medial and lower pressures posterior and lateral (Fig. 23-2). Contraction and relaxation are primarily mediated by two neurotransmitters, acetylcholine (excitatory) and nitric oxide (inhibitory). Relaxation can also occur when tonic vagal cholinergic excitation is inhibited with deglutition.

Pathophysiology of GERD

Gastroesophageal reflux occurs when LES pressure is less than that of intragastric pressure. This can occur under both normal and pathophysiologic conditions.

Immediately after swallowing, LES pressure decreases to allow food passage from the esophagus into the stomach. While normally maintained in a tonically contracted state, LES pressure also decreases temporarily, during transient lower esophageal sphincter relaxation (TLESR). This relaxation is a spontaneous, non–swallow-induced, vagally-mediated reflex associated with relaxation of the crural diaphragm.\textsuperscript{17,18} When the gastric fundus is distended with gas, TLESR allows for belching to relieve elevated intragastric pressure. Increased frequency or duration of TLESR can predispose to reflux, accounting for up to 40\% of abnormal reflux in patients with a normal LES.\textsuperscript{19} The majority of reflux episodes occur during TLESR in the setting of normal resting LES pressure.\textsuperscript{18,20} Most of the remainder of reflux episodes occur due to increased intra-abdominal pressure coupled with low resting LES pressure.\textsuperscript{18} Increased gastric distention from largest intragastric volume, such as after a large meal, decreases LES length, thereby decreasing the pressure threshold required for pathologic reflux.

LES pressures naturally vary during the migrating motor complex while fasting.\textsuperscript{21} LES pressure also drops frequently due to secretion of hormones secondary to food ingestion (cholecystokinin [CCK], secretin)\textsuperscript{22,23} and pregnancy (progesterone).\textsuperscript{24} The nature of food composition can also affect LES pressure. Substances known to cause decreases in LES pressure include chocolate, alcohol, caffeine, and fats.\textsuperscript{23,25–27} Other lifestyle related considerations, including smoking, can also lower LES pressure and predispose to reflux.\textsuperscript{28}

Presentation

Symptoms of gastroesophageal reflux can be categorized as “typical” or “atypical.” Typical symptoms include heartburn, regurgitation, water brash, and, when advanced, dysphagia. While considered a typical symptom,
dysphagia warrants investigation for potential complications including an underlying motility disorder, stricture, ring, or malignancy. Atypical symptoms, on the other hand, include cough, globus sensation, hoarseness, throat clearing, asthma, aspiration pneumonia, pulmonary fibrosis, and atypical chest pain (Table 23-1).

### TABLE 23-1: PRESENTATION OF GERD

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heartburn</td>
<td>1. Throat clearing</td>
</tr>
<tr>
<td>Daily: 2-9%</td>
<td>2. Hoarse voice</td>
</tr>
<tr>
<td>Weekly: 8-18%</td>
<td>3. Chronic cough</td>
</tr>
<tr>
<td>Monthly: 13-36%</td>
<td>4. Asthma</td>
</tr>
<tr>
<td>2. Regurgitation</td>
<td>5. Chest pain</td>
</tr>
<tr>
<td>3. Waterbrash</td>
<td>6. COPD</td>
</tr>
<tr>
<td>4. Dysphagia(^a)</td>
<td>7. Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>8. Aspiration pneumonia</td>
</tr>
<tr>
<td></td>
<td>9. Globus sensation</td>
</tr>
</tbody>
</table>

\(^a\)37% in erosive esophagitis

### GERD and Quality of Life

In 1948, the World Health Organization (WHO) defined health as being more than simply absence of disease, recognizing that it incorporates not only physical but also psychological and social components. Quality of life (QoL) surveys reveal that GERD patients are equally or more impaired with regard to several aspects of QoL than patients with major medical comorbidities, including hypertension and diabetes, and more impaired with regard to bodily pain than patients with major depression.\(^{29}\) Even in the absence of medical comorbidities, GERD results in impaired functioning and well-being when compared with healthy controls.\(^{30}\) Health-related quality of life (HRQoL) models, designed to specifically examine the effect of a given disease state on a patient’s well-being, support the notion that GERD has a significant impact that is not captured by traditional physiologic testing.\(^{31}\)
Specifically, frequency and number of symptoms are inversely related to QoL scores. Timing of symptoms also correlates with QoL, with presence of nocturnal symptoms resulting in decreased reported QoL compared to patients with only daytime symptoms. While symptom severity is not related to presence or absence of pathologic evidence of reflux, it is related to QoL. Correspondingly, QoL scores are not correlated with presence or absence of pathologic extent of disease.

Considering the importance of QoL as demonstrated above, the primary goals of GERD treatment include symptom relief in addition to prevention of complications and healing of esophagitis. From a patient’s standpoint, however, relief of symptoms may be considered paramount. Consistent with improvement in symptoms, medical therapy improves QoL scores in GERD patients irrespective of presence of pretreatment pathologic evidence of GERD. While medical treatment results in improved QoL scores, evidence for superiority of one medical modality over another is lacking. Similarly, surgical intervention has consistently, across numerous studies, been shown to improve QoL scores in patients suffering from GERD. In some studies, surgery has even resulted in QoL scores approximating those of healthy controls. Initial reports suggesting equivalence of open surgical intervention to optimal medical management for improvement in QoL have since been substantiated. Evidence for superiority of open surgery over medical therapy, however, is lacking. Laparoscopic surgery, on the other hand, has been shown to significantly improve QoL when compared to no treatment or proton pump inhibitor (PPI) therapy. Laparoscopic fundoplication has been shown to be a very durable operation, with more than 90% of patients having excellent results for as long as 20 years after the operation.

As QoL has a significant subjective component, and symptom severity is correlated with patient quality of life, it is imperative to consider QoL as a primary endpoint in GERD therapy, be it medical or surgical.

**COMPLICATIONS**

Complications of GERD are classified as mucosal, extraesophageal/respiratory, or metaplastic/neoplastic. These complications are the direct result of mucosal or epithelial exposure to gastric contents (acid or alkali) and the host’s natural response to the damage caused by that
exposure.

**Mucosal**

Mucosal complications include esophagitis and esophageal stricture. Esophageal mucosa is damaged when exposed for prolonged periods of time to the contents of reflux of highly acidic or alkaline nature. Ingredients proposed to play a role in the process include gastric acid, pepsin, pancreatic enzymes, and bile acids. Prevalence of mucosal complications has been shown to be higher in patients with combined acid and alkaline reflux compared to those with only acid reflux. The most severe injuries are reported in the presence of acid, pepsin, and bile salt exposure.

Although not strong, there is some correlation with endoscopic esophagitis severity and symptom severity. Acid exposure often leads to more pain but less mucosal damage, with alkaline exposure leading to more mucosal damage despite less pain. Reflux of more than just acidic contents is more common in patients with mucosal and metaplastic/neoplastic complicated GERD, explaining why medical therapy with PPIs alone is not always effective. Nevertheless, PPI therapy may improve esophagitis in up to 90% of patients, but relapse may occur in up to 80% within 1 year of medication discontinuation.

The incidence of esophageal stricture in patients with esophagitis is 10% to 25%, with one large Veterans Administration (VA) study reporting a 14% incidence. Treatment for patients with stricture should start with PPIs, but many patients require repeated esophageal dilations to control dysphagia. Stricture patients may benefit from antireflux surgery by decreasing the need for further dilations and dysphagia. If a stricture is found on endoscopy, a biopsy should be obtained to rule out malignancy.

**Metaplastic/Neoplastic**

Barrett esophagus (BE) is a metaplastic consequence of GERD involving a change from normal squamous epithelial lining to a segment of columnar epithelial lining that predisposes to the development of adenocarcinoma of the esophagus. This is discussed later in this chapter.
Extraesophageal Manifestations: Laryngopharyngeal Reflux and Pulmonary Consequences

Many of the atypical symptoms of GERD, including cough, recurrent pneumonia, asthma, COPD, laryngitis, and pulmonary fibrosis, are secondary to the effects of reflux on extraesophageal aerodigestive tract. Up to 30% to 50% of patients with asthma, and nearly 90% of patients with pulmonary fibrosis, have objective evidence of GERD.\(^{43-45}\) Gastric acid aspiration can be a mechanism for respiratory symptoms related to GERD.\(^{46,47}\) Another proposed mechanism is vagally-mediated bronchoconstriction, in which acid exposure in the esophagus induces bronchoconstriction, possibly through vagal nerve networks innervating both the esophagus and bronchial tree.\(^{48}\) A relationship between GERD and respiratory symptom severity has been established.\(^{43}\)

Patients presenting with poorly controlled or adult-onset asthma may benefit from an evaluation for GERD as a potential underlying cause or exacerbating factor in their respiratory disease. Upper endoscopy and ambulatory pH monitoring should be performed to document mucosal evidence of GERD and to attempt to temporally correlate extraesophageal symptoms with reflux events. Multichannel intraluminal impedance-pH (MII-pH) shows some promise in the documentation of reflux and correlation with extraesophageal symptoms.\(^{38}\) A trial of PPI therapy is a reasonable initial treatment for suspected GERD-related respiratory symptoms. If symptoms improve, this may strengthen the notion that GERD is at least partially responsible for the patient’s symptoms. In general, however, it is difficult to establish the association of acid reflux to extraesophageal symptoms in the absence of the typical symptoms of GERD. Surgery for these patients should be approached with caution.

Mimics of GERD

Typical symptoms of GERD, including heartburn, regurgitation, and dysphagia, are nonspecific and present in several pathologic conditions. Therefore, systematic evaluation of the patient presenting with esophageal
symptoms is necessary to achieve proper diagnosis and management. Optimal management of the patient with esophageal symptoms requires distinguishing those with GERD from those with esophageal motility disorders and functional esophageal disorders. However, the physician needs to be aware that there are nonesophageal causes of chest pain, the most concerning of which is cardiac ischemia, such as angina pectoris. Mediastinal inflammatory diseases and neoplasms occasionally present as chest pain. A careful history and physical examination can differentiate these processes.

Esophageal motility disorders encompass any abnormality of the usually coordinated peristaltic activity of the esophagus. They can be classified as primary or secondary based on the underlying cause of the abnormal motility. Primary esophageal motility disorders are the result of impaired excitatory or inhibitory innervations of the LES and body of the esophagus. These include achalasia, diffuse esophageal spasm, nutcracker esophagus, hyper- and hypotensive LES, ineffective esophageal motility, and nonspecific esophageal motility disorders. The most common symptoms of achalasia and other primary esophageal motility disorders are chest pain and dysphagia, which as mentioned earlier are also frequently seen as presenting symptoms in GERD. In fact, a large proportion of patients eventually diagnosed with esophageal motility disorders are initially presumptively diagnosed with GERD.49

Malignancy, while not a primary disorder of esophageal motility or LES function, can also present in similar fashion to GERD. While GERD and distal esophageal adenocarcinoma have a well-established relationship,50 unrelated malignancies of the gastric cardia and more remote regions such as the pancreas, lung, and kidney can also produce a condition that may present in similar fashion to GERD. Pseudoachalasia, thought to be due to compression of the LES by tumor, infiltration of myentric plexus and/or vagus nerves, and paraneoplastic neuropathy without direct infiltration, presents with progressive dysphagia to solids and liquids, as can also been seen as GERD symptoms.51

Functional esophageal disorders are a group of conditions marked by symptoms of apparent esophageal origin without objective evidence of esophageal pathology. They mimic GERD in esophageal symptoms, but diagnostic evaluation reveals normal endoscopy, manometry readings, and pH values by ambulatory or impedance pH testing.52 As such, they remain a
diagnosis of exclusion after ruling out GERD, malignancy, and esophageal motility disorders by the aforementioned tests. The four currently recognized functional esophageal disorders, as outlined by the Rome III Consensus Criteria, are functional heartburn, functional chest pain of presumed esophageal origin, functional dysphagia, and globus. Diagnostic algorithms have been proposed by multiple groups, but generally involve a progression of objective tests, including endoscopy, esophageal motility studies, PPI trial, and pH monitoring to rule out other esophageal pathology. Initial tests should be directed by the presenting symptom, and subsequent testing guided by results of the previous test.

**Diagnostic Evaluation**

Effective treatment of GERD, aimed at prevention of its complications and improvement in patient QoL, requires accurate diagnosis. Symptoms experienced by patients with GERD are not always specific, and could result in improper or ineffective treatment. Following a comprehensive history and physical examination, in patients with typical symptoms of heartburn but without “alarm” symptoms, a trial of PPI is reasonable. The alarm symptoms of dysphagia, odynophagia, weight loss, anemia, or signs of bleeding require further evaluation. For those patients who have alarm symptoms or who are considering surgical intervention, mandatory objective testing includes upper endoscopy, esophageal manometry, and esophageal pH monitoring. Additional testing may include contrast esophagography, impedance pH monitoring, gastric emptying scintigraphy, laryngoscopy, and bronchoscopy.

The American College of Gastroenterology recently released a set of evidence-based clinical guidelines for the diagnosis and management of GERD. A presumptive diagnosis of GERD is often made based on a history of typical symptoms. However, the presence of heartburn and regurgitation symptoms had a sensitivity of only 30% to 76% and specificity of 62% to 96% for the presence of erosive esophagitis. A PPI trial to “confirm” a diagnosis of GERD by symptom response increases sensitivity to 78%, with a specificity of 54%. Chest pain, which can be the presenting symptom of GERD, should prompt an evaluation to exclude a cardiac etiology. Once a cardiac source has been eliminated and prior to PPI administration,
endoscopic evaluation and pH monitoring should be performed to document the presence of GERD, as PPI response compared to placebo is minimal in the absence of documented GERD.\textsuperscript{57}

**CONTRAST ESOPHAGOGRAPHY**

Contrast esophagography is a useful test to anatomically evaluate the esophagus and gastroesophageal junction. It can evaluate esophageal emptying and occurrence of reflux and detect the presence of hiatal hernia and the presence and location of complications such as strictures, webs, ulcers, or masses. It is a relatively poor test of esophageal motility. Contrast esophagography should be employed as the first step in evaluation of alarm symptoms such as dysphagia. Even high-quality esophagograms have been shown to have low sensitivity for detecting GERD and signs of esophagitis. It should be noted that GERD cannot be reliably ruled out solely by esophagography, but that it serves as a useful complement to other objective tests. Contrast esophagography is an excellent test to evaluate the presence and size of paraesophageal hernia.

**UPPER ENDOSCOPY**

Endoscopic evaluation is the primary modality for evaluating esophageal mucosa and also allows for direct visualization of the stomach and duodenum. It can assess for structural issues such as size of a hiatal hernia or localization of pathology.

Presence and severity of esophagitis is most commonly graded according to the Los Angeles (LA) classification (Table 23-2).\textsuperscript{58,59} LA grade A is considered to be the presence of one or more mucosal breaks that are less than or equal to 5 mm in length. Grade B is defined as the presence of one or more mucosal breaks longer than 5 mm. Grade C involves one or more mucosal breaks that are continuous between the apices of two or more mucosal folds, but that encompass less than 75% of the esophageal circumference. Lastly, LA grade D includes continuous breaks between mucosal folds encompassing greater than 75% of the esophageal circumference. In the presence of erosive esophagitis, when using LA classification, specificity of endoscopy for diagnosis of GERD is high, with good interobserver correlation.\textsuperscript{59}
Nonerosive esophagitis is more difficult to diagnose visually by endoscopy, but may be detected by microscopic findings on mucosal biopsy, including eosinophils, lymphocytes, polymorphonuclear leukocytes, and balloon cells. Biopsy has been found to have poor sensitivity (62%) and specificity (27%) when using a threshold of one or more histologic abnormalities consistent with esophagitis. Specificity is significantly increased (91%) and sensitivity decreased (31%) when using a threshold of three histologic abnormalities. Despite the high specificity, routine use of esophageal biopsy in the face of endoscopically normal appearing mucosa is not currently recommended.

Lastly, via retroflexion of the endoscope after passage through the GEJ, abnormalities of the LES flap valve can be identified and graded according to the Hill classification (Fig. 23-3). Increasing abnormality of the gastroesophageal flap valve (increasing Hill grade) has been correlated with increased prevalence of a mechanically defective sphincter, abnormal esophageal acid exposure, erosive esophagitis, and BE.

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**TABLE 23-2: LOS ANGELES (LA) CLASSIFICATION OF EROSIONAL ESOPHAGITIS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≥1 mucosal break ≤5 mm in length</td>
</tr>
<tr>
<td>B</td>
<td>≥1 mucosal break &gt;5 mm in length</td>
</tr>
<tr>
<td>C</td>
<td>≥1 mucosal break continuous between apices of ≥2 mucosal folds, encompassing &lt;75% of esophageal circumference</td>
</tr>
<tr>
<td>D</td>
<td>continuous breaks between mucosal folds encompassing &gt;75% of esophageal circumference</td>
</tr>
</tbody>
</table>
FIGURE 23-3 Hill classification of the gastroesophageal junction. A. Grade I flap valve appearance. Note the ridge of tissue that is closely approximated to the shaft of the retroflexed endoscope. It extends 3–4 cm along the lesser curve. B. Grade II flap valve appearance. The ridge is slightly less well defined than in grade I and it opens rarely with respiration and closes promptly. C. Grade III flap valve appearance. The ridge is barely present, and there is often failure to close around the endoscope. It is nearly always accompanied by a hiatal hernia. D. Grade IV flap valve appearance. There is no muscular ridge at all. The gastroesophageal valve stays open all the time, and squamous epithelium can often be seen from the retroflexed position. A hiatal hernia is always present. (Reproduced with permission from Hill LD, Kozarek RA, Kraemer SJ, et al: The gastroesophageal flap valve: in vitro and in vivo observations, Gastrointest Endosc 1996 Nov;44(5):541-547.)

ESOPHAGEAL MANOMETRY

Esophageal manometry is a catheter-based system to measure esophageal pressures. Manometry was originally developed using water-based hollow
catheters measuring pressure waves at distinct 5-cm intervals in the esophagus (Fig. 23-4). These measurements included the upper esophageal sphincter, points along the esophageal body, and the LES. This older technology is now supplanted by high-resolution manometry (HRM). In HRM, a solid-state catheter with a sevenfold increase in the number of sensors at 1-cm intervals provides for a more “continuous” measurement of pressures along the length of the esophagus. These readings are converted by the system’s computer program into a color topography (Fig. 23-5). Manometric evaluation is essential in the preoperative evaluation of any patient considering antireflux surgery. It will identify patients who may have symptoms suggestive of GERD but really are suffering from some other motility disorder, such as achalasia or scleroderma. This test may also help direct surgical approach, identifying patients who would be better candidates for partial, rather than complete, fundoplication, for instance in the case of manometric evidence of hypomotility.

FIGURE 23-4 Esophageal manometry pressure waves.
FIGURE 23-5 High-resolution manometry image.

LES competency has been defined based on comparative manometry studies of healthy volunteers and patients with GERD symptoms. The ability of the LES to properly function to protect the esophageal mucosa from exposure to gastric juice depends on its resting pressure, overall length, and the subcomponent of intra-abdominal length. Each HRM system will have slightly different normal pressure values, depending on the calibration of the system. However, an LES is considered to be incompetent if one or more of these anatomic components is abnormal, or more specifically, an average LES pressure less than 6 mm Hg, average overall length of 2 cm or less, and intra-abdominal length of 1 cm or less. Although a “hypotensive” LES supports the diagnosis of GERD, it is not essential. Many patients with pathologic reflux may have normotensive LES.

Measurement of esophageal body peristalsis is vital. A patient with normal peristaltic waves and pressures is the ideal candidate for a fundoplication. Ineffective esophageal motility is 30% or more swallows leading to failed peristalsis, or a mean wave pressure of less than 30 mm Hg (Table 23-3).
Preoperative assessment of esophageal motility is vital in determining whether a fundoplication is appropriate, and may help in tailoring the type of fundoplication.

**TABLE 23-3: INFORMATION FROM HIGH RESOLUTION MANOMETRY WITH NORMAL RANGES**

<table>
<thead>
<tr>
<th>Information</th>
<th>Normal Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal Pressures</strong></td>
<td></td>
</tr>
<tr>
<td>LES, respiratory mean (mm Hg)</td>
<td>13-43</td>
</tr>
<tr>
<td>UE, mean (mm Hg)</td>
<td>34-104</td>
</tr>
<tr>
<td><strong>Residual Pressures</strong></td>
<td></td>
</tr>
<tr>
<td>LES, mean (mm Hg)</td>
<td>&lt;15</td>
</tr>
<tr>
<td>UES, mean (mm Hg)</td>
<td>&lt;12</td>
</tr>
<tr>
<td><strong>Anatomy</strong></td>
<td>N/A</td>
</tr>
<tr>
<td>LES proximal (cm)</td>
<td>N/A</td>
</tr>
<tr>
<td>LES intra-abdominal (cm)</td>
<td>N/A</td>
</tr>
<tr>
<td>Esophageal length</td>
<td>N/A</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td></td>
</tr>
<tr>
<td><strong>Motility</strong></td>
<td></td>
</tr>
<tr>
<td>Distal wave amplitude (mm Hg)</td>
<td>43-153</td>
</tr>
<tr>
<td>Distal contractile integral (mm Hg-cm-s)</td>
<td>500-5000</td>
</tr>
<tr>
<td>Incomplete bolus clearance (%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**AMBULATORY pH MONITORING**

Ambulatory pH monitoring is the gold standard for diagnosis of GERD. It directly measures esophageal acid exposure, frequency and duration of reflux episodes, and concordance with the patient’s symptoms (Fig. 23-6). Both 24- and 48-hour ambulatory pH monitoring tests have excellent sensitivity (77%-100%) and specificity (85%-100%) in the setting of erosive esophagitis. In patients without endoscopic evidence of erosive esophagitis, sensitivity is decreased to closer to 70%, but is as high as 90% when
combined with impedance.\textsuperscript{66}

\textbf{FIGURE 23-6} Twenty-four-hour esophageal pH monitoring.

Nevertheless, there are excellent positive and negative predictive values of 96%, and overall accuracy of 96% for 24-hour esophageal pH monitoring for the diagnosis of GERD.\textsuperscript{67}

Patients should be counseled to discontinue any antisecretory medications 2 weeks prior to initiating pH monitoring to increase the ability to correlate symptoms with reflux events and grade the severity of disease. An abnormal pH test and good temporal correlation between symptoms and reflux episodes is the best predictor of successful outcome after antireflux surgery.

Early-generation esophageal pH monitoring devices involved passage of a catheter-based pH electrode transnasally. Patient comfort has been improved by the development of wireless pH capsules that transmit information to an external receiver.\textsuperscript{68} Readings from the transnasal catheter can be negatively affected by the patient decreasing potentially provocative activities, leading to false negative results, and esophageal shortening during deglutition, noted to be up to 2 cm in length, can cause positional changes of the pH probe, leading to false positive results as the electrode moves closer to the GEJ.\textsuperscript{69} However, non-acid reflux, known to be an important factor in development of esophagitis and other extraesophageal complications of GERD, is not detected by traditional pH monitoring. In addition, there may be an increase in acid exposure on day 2 of monitoring, thus potentially decreasing the sensitivity of 24-hour testing.\textsuperscript{70} The development of wireless pH monitoring
systems has improved patient comfort and allowed for extension of monitoring to 48 hours or longer in some cases, increasing the sensitivity of the test.68

The DeMeester score (Table 23-4) has long been the standard by which results of 24-hour pH monitoring are reported.71 The score is determined by six variables evaluating frequency and severity of reflux, and the ability of the esophagus to clear acid. These variables include total number of reflux events, percentage of total time spent in an acid environment with a pH less than 4, percentage of upright time spent in an acid environment with a pH less than 4, percentage of supine time spent in an acid environment with a pH less than 4, duration of longest reflux episode, and number of reflux episodes lasting more than 5 minutes.

<table>
<thead>
<tr>
<th>Components Measured</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of reflux events</td>
<td>104</td>
</tr>
<tr>
<td>Total time spent in an acid environment, pH&lt;4 (%)</td>
<td>4.9</td>
</tr>
<tr>
<td>Upright time spent in an acid environment, pH &lt;4 (%)</td>
<td>7.3</td>
</tr>
<tr>
<td>Supine time spent in an acid environment, pH &lt;4 (%)</td>
<td>1.4</td>
</tr>
<tr>
<td>Duration of longest reflux episode (min)</td>
<td>16</td>
</tr>
<tr>
<td>Number of reflux episodes lasting more than 5 min</td>
<td>5</td>
</tr>
<tr>
<td>Composite DeMeester score</td>
<td>14.72</td>
</tr>
</tbody>
</table>

**MULTICHANNEL INTRALUMINAL IMPEDANCE-pH MONITORING**

Similar to traditional 24-hour pH monitoring, MII-pH involves a transnasal catheter-based system and is thus often limited by patient comfort. This modality does, however, provide the benefit of allowing for concomitant measurement of bolus movement and pH by use of multiple electrodes.
positioned serially along a catheter. By incorporating simultaneous pH and impedance monitoring, this modality allows for determination of the character of reflux episodes (acid vs non-acid), a measurement not possible with traditional catheter-based pH monitoring. While this theoretically provides a distinct advantage over other modalities, clinical advantages remain under investigation.

Figures 23-7 and 23-8 provide evaluation algorithms for patients with typical and atypical symptoms of GERD. Once again, it needs to be emphasized that antireflux surgery for patients with only atypical symptoms of GERD should be considered with extreme caution. There are many gastroenterologists and surgeons who would not offer these patients antireflux surgery under any circumstances.

**FIGURE 23-7** Evaluation of the typical symptoms of gastroesophageal reflux disease.
Measuring Symptom Severity and Quality of Life

In typical practice, most clinicians simply enumerate the symptoms with quality descriptors of severity. Although this gives some impression of how GERD affects a patient, it does not quantitate the level of this affect. QoL and symptom severity instruments are used for this purpose. In general, QoL instruments are divided into generic and disease-specific instruments.

GENERIC INSTRUMENTS USED IN GERD

Generic QoL instruments are broadly applicable to a variety of disease processes. They measure different QoL domains. Table 23-5 lists generic instruments that have been used in GERD patients with the domains they measure.
### TABLE 23-5: EXAMPLES OF QUALITY-OF-LIFE INSTRUMENTS USED TO MEASURE PATIENT-PERCEIVED EFFECTS OF GERD

<table>
<thead>
<tr>
<th>Type of Instrument</th>
<th>Name of Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>SF-36</td>
</tr>
<tr>
<td></td>
<td>Psychological General Well-Being (PGWB)</td>
</tr>
<tr>
<td>Disease-specific/symptom severity</td>
<td>Digestive Symptoms and Impact Questionnaire</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal Reflux Disease-Health Related Quality of Life Scale</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal Reflux Disease Symptom Assessment Scale</td>
</tr>
<tr>
<td></td>
<td>GERD Symptom Frequency Questionnaire</td>
</tr>
<tr>
<td></td>
<td>Heartburn Specific Quality of Life Instrument</td>
</tr>
<tr>
<td></td>
<td>Nepean Dyspepsia Index</td>
</tr>
<tr>
<td></td>
<td>Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index</td>
</tr>
<tr>
<td></td>
<td>Patient Assessment of Upper Gastrointestinal Disorders Quality of Life</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Symptom Rating Scale</td>
</tr>
<tr>
<td></td>
<td>Quality of Life in Reflux and Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Quality of Life Questionnaire in Gastroesophageal Reflux</td>
</tr>
</tbody>
</table>

**DISEASE-SPECIFIC/SYMPOTMS SEVERITY**

Disease-specific instruments measure aspects of QoL that are specifically affected by the disease. For GERD, it may include such things as sleep, work, pain, eating habits, etc. Symptom severity instruments measure the symptoms specific for the disease. For GERD, this would include heartburn, regurgitation, dysphagia, etc. for typical symptoms, and hoarseness, cough, wheezing, etc. for atypical symptoms (Table 23-5).
Evaluation of studies of the treatments of GERD should include some measures of QoL and symptom severity, as most treatments are designed to improve symptoms. Some practitioners use these instruments routinely in clinical practice for both documenting the magnitude of change caused by an intervention and inpatient counseling.

Management

Management of GERD can be broadly categorized into lifestyle modifications, medical, and surgical.

In 2006, a systematic review of the effect of lifestyle modifications on lower esophageal sphincter pressure, esophageal pH, and GERD symptoms revealed that intake of several products, including tobacco, chocolate, and carbonated beverages, led to decreased LES pressure. Esophageal acid exposure increased with consumption of tobacco, alcohol, chocolate, and fatty foods, but cessation of tobacco and alcohol had no physiologic effect on LES pressure and did not lead to subjective symptom improvement. However, weight loss has been correlated with reduction in GERD symptoms. Elevating the head of the bed leads to improvements in symptoms and pH monitoring values. Aside from this, there is little evidence in support of lifestyle modification strategies as durable and effective antireflux therapy.

The success of medical therapy has made it a mainstay of treatment for GERD. For those failing lifestyle modifications alone, medical therapy can take the form of antacids, histamine receptor antagonists, or PPIs. PPI therapy has been shown to have higher rates of healing and decreased relapse rates when compared to histamine receptor antagonists in patients with erosive esophagitis. In fact, meta-analysis has demonstrated healing of erosive esophagitis inclusive of all grades to be approximately 84% with PPIs, 52% with histamine receptor antagonists, 39% with sucralfate, and merely 28% with placebo. While there are many currently available PPIs, no one drug is superior to any other for symptom relief. Overall, partial relief of GERD symptoms has been found in 30% to 40% of patients after an 8-week trial of PPI therapy, without any difference shown between once- or twice-daily dosing. Risk factors for poor response include hiatal hernia, extraesophageal symptoms, longer duration of symptoms, and lack of
compliance.\textsuperscript{81} Sixty-six percent to 75\% of patients with NERD, and 90\% to 100\% with erosive esophagitis, will demonstrate relapse of symptoms at 6 months after discontinuing PPI therapy.\textsuperscript{82,83} Therefore, maintenance PPI therapy is recommended.

While medical therapy has proven fairly successful and leads to symptom improvement in a significant number of patients, it does not address the pathophysiologic component of a mechanically defective LES, a factor that can only be dealt with by surgical or endoscopic therapy.

**SURGICAL THERAPY**

The history of antireflux surgery began in 1956 with the first report of successful operative intervention by Nissen.\textsuperscript{84} Since this initial report, techniques and approaches to antireflux surgery have been modified several times and evolved along with surgical technology. After Nissen’s original description, Dor\textsuperscript{48} and Toupet\textsuperscript{85} later developed and described variations of the procedure involving partial anterior and posterior fundoplications to avoid bloating. Belsey developed a transthoracic partial repair, which required several modifications until settling on the Mark IV. Complete mobilization of the gastric fundus via division of the short gastric vessels was subsequently described by DeMeester et al. in 1986.\textsuperscript{86} Finally, Dallemagne et al. in 1991 reported the first successful laparoscopic Nissen fundoplication.\textsuperscript{87}

Indications for surgical therapy in GERD include incomplete symptomatic relief from medical therapy, desire to discontinue medical therapy, medical noncompliance, side effects of medical therapy, esophagitis refractory to medical therapy, presence of symptoms specifically related to a hiatal hernia, and esophageal and extraesophageal complications. Several studies have directly compared surgical and medical therapy for GERD (Table 23-6). The VA GERD Study Group Trial, a randomized controlled trial with 10-year follow-up, showed superiority of surgery over histamine receptor blockade and lifestyle modification for typical symptoms and esophagitis in the veteran population.\textsuperscript{88} Another randomized controlled trial showed less acid exposure at 3 months and improved well-being scores at 1 year in patients undergoing surgical versus PPI therapy.\textsuperscript{89}
Data concerning cost-effectiveness of surgical versus medical therapy remain inconclusive. A systematic review of Medline, EMBASE, and Cochrane databases published in 2011 revealed higher costs for surgical therapy, but two studies included in the review reported more quality-adjusted life-years with surgery.\(^{90}\) Also of note, meta-analysis of health-related and GERD-specific QoL aspects from randomized controlled trials of surgical (open or laparoscopic) versus medical treatment of GERD showed less frequent symptoms and higher patient-reported levels of satisfaction after surgical intervention despite a significant proportion of patients requiring continued medical therapy after fundoplication.\(^{91}\)

Surgical intervention for GERD is aimed at fixing the structural defects contributing to the pathophysiology while minimizing dysphagia, bloating, and vagally mediated adverse events. As such, the intervention must be designed to restore adequate LES pressure, the interaction between the esophagus and diaphragmatic hiatus and 2 cm of intra-abdominal length, while allowing for normal passage of ingested materials through the GEJ, and eventually from the stomach to the small bowel. This is generally accomplished by reduction of the intrathoracic portion of the stomach and esophagus with the hiatal hernia, repair of the diaphragmatic hiatal defect, and a fundoplication procedure in which the gastric fundus is used to create a “wrap” around the distal esophagus. The fundus creates a functional augmentation to the LES, as it is vagally innervated and will relax normally with deglutition in the absence of intraoperative vagal injury.
PRIMARY ANTIREFLUX REPAIRS

Principles. Antireflux operations can be performed via a laparoscopic, open laparotomy, thoracoscopic, or open thoracotomy approach. Thoracic approaches are no longer routinely done, but may be needed for special circumstances. The 360-degree Nissen fundoplication is currently the most commonly performed antireflux procedure in the United States. Partial fundoplications are essentially variations of this procedure, but all must adhere to a certain set of key principles for successful outcomes. The first principle is dissection of the hiatus for adequate visualization of the left and right crura. The surgeon must take care to preserve the vagal nerves. The anterior vagal nerve generally lies adherent to the anterior surface of the esophagus, while the posterior nerve is a variable distance away in the fat posterior to the esophagus. The second principle is mobilization of the gastric fundus to provide for a tension-free fundoplication. Although this generally requires division of the short gastric vessels in the gastrosplenic ligament, this is not mandatory. The third principle is performing enough circumferential esophageal dissection to allow for mobilization of 2.5 to 3 cm of intra-abdominal esophagus. Fourth is posterior crural approximation to repair the hiatal hernia but allow for adequate esophageal expansion during swallowing. Lastly, the fundoplication itself should be constructed over a dilator of adequate size so that the fundoplication is floppy and about 2 cm in length.

Laparoscopic and Open Nissen Fundoplication. After induction of general anesthesia, the patient should be placed supine in a low lithotomy position, the so-called “French” position, with reverse Trendelenburg positioning employed as needed to allow the abdominal viscera to fall away from the surgical field. Although there are a variety of port placement positions depending on surgeon preference, the key is to allow for a camera port, liver retractor, two working ports, and a retraction port as needed. Our preferred port placement is shown in Figure 23-9. If an open approach is required, our preference is an upper midline incision.
The surgeon operates from between the patient’s legs while assistants are positioned to the patient’s right and left. To gain access to the posterior mediastinum, the gastrohepatic omentum at the pars flaccida (the so-called “window of Heister”) is first opened and divided from its attachment to the hiatus (Fig. 23-10). The right crus should be immediately identified. The phrenoesophageal ligament is divided to expose the esophagus, and this division is taken to the left to expose the left crus. The space between the esophagus and crus is developed posterior to the angle of His (Fig. 23-11). This dissection should be carried as posteriorly and inferiorly as possible to ease creation of the retroesophageal space. Similarly, the phrenoesophageal ligament is divided between the esophagus and the right crus and this space is developed. This allows for circumferential exposure of the esophagus at the hiatus. Care should be taken to identify the possibility of an accessory left hepatic artery branching from the left gastric artery to avoid injury. As the phrenoesophageal membrane is then opened on the right and dissection carried anteriorly, care must be taken to identify and avoid injury to both
anterior and posterior vagal branches. Posterior retroesophageal dissection is carried out until the union of the right and left crura is identified. At this point, the retroesophageal window is developed (Fig. 23-12). Once the posterior esophageal window is completed, a Penrose drain is passed posterior to the esophagus and the two ends secured (Fig. 23-13). The drain is used to manipulate the esophagus during the operation. Circumferential mediastinal dissection should be carried out until at least 3 cm of esophagus is present within the abdominal cavity without tension. If undue tension prevents adequate esophageal mobilization, a lengthening procedure such as a Collis gastroplasty, described later, should be considered. Once esophageal mobilization or lengthening is completed, the crura are approximated posteriorly using interrupted nonabsorbable sutures over Teflon pledgets, although the pledgets are not mandatory (Fig. 23-14). Crural closure should be up to the esophagus but allow for passage of a laparoscopic instrument or small dilator to minimize the risk of stenosis. The short gastric vessels are then divided along the greater curvature of the stomach from the inferior pole of the spleen, allowing for exposure of the posterior stomach and division of the posterior gastric vessels.
FIGURE 23-10 Division of the window of Heister and phrenoesophageal ligament.

FIGURE 23-11 Dissection of the plane between the left crus and esophagus.
FIGURE 23-12 Development of the retroesophageal space.

FIGURE 23-13 Use of a Penrose drain to encircle the esophagus.
Attention is then turned to creation of the fundoplication. The fundus is grasped on the posterior surface passed posterior to the esophagus through the retroesophageal window such that the greater curvature will become juxtaposed to the left side of the esophagus (Fig. 23-15). This allows for the fundus to be invaginated around the esophagus to avoid a “twisted” wrap. The surgeon may pull the fundus back and forth in a so-called “shoeshine maneuver” to ensure that the stomach is not twisted and that there is adequate mobility to create a tension-free fundoplication. A 56 to 60 Fr dilator should be passed through the gastroesophageal junction while creating the wrap to ensure that the wrap is not excessively tight. The anterior surface of fundus at the greater curvature is brought anterior to the esophagus. A fundoplication of approximately 2 cm in length is then created around the distal esophagus just superior to the gastroesophageal junction by securing the right and left limbs of the fundus anteriorly along the greater curvature using two pledgeted polypropylene sutures (although some surgeons prefer braided suture), incorporating full thickness stomach and partial thickness right lateral esophageal wall with each suture. The fundoplication should be pointed to the patient’s right, ensuring that there are equal lengths of the wrap anteriorly and posteriorly (Fig. 23-16). Special care should be taken to avoid incorporation of the anterior vagus nerve in the sutures. Finally, intraoperative upper endoscopy is performed to confirm proper position and construction of the fundoplication (Fig. 23-17).
FIGURE 23-15 The gastric fundus being brought posterior to the esophagus.
FIGURE 23-16  Construction of the Nissen fundoplication.
Collis Gastroplasty. A Collis gastroplasty can be constructed if there is concern about a foreshortened esophagus. This is vital, as a foreshortened esophagus is a cause of recurrent transdiaphragmatic herniation. In this procedure, a continuation of the distal esophagus, or neoesophagus, is created from a tubularized portion of stomach. There are two methods of constructing a Collis gastroplasty.

In one method, an esophageal dilator is passed into the stomach along the lesser curvature. The anvil of an EEA stapling device is passed through the posterior surface of the stomach and then through the anterior surface about 2 to 3 cm from the angle of His at the left lateral border of the dilator. A gastric window is created in the fundus when the staple is fired and the donuts removed. Through the window, a linear cutting stapler is then placed and

FIGURE 23-17  Endoscopic view of completed Nissen fundoplication showing the normal “stacked coils” appearance.
deployed parallel to the dilator. When fired, it creates a tubular esophageal extension from gastric tissue. The Nissen fundoplication is then performed around this neoesophagus (Fig. 23-18).

FIGURE 23-18 Construction of a Collis gastroplasty using an EEA stapled technique. (Reproduced with permission from Horvath KD, Swanstrom LL, Jobe BA: The short esophagus: pathophysiology, incidence, presentation, and treatment in the era of laparoscopic antireflux
The other method of creating a Collis neoesophagus is the wedge gastroplasty. In this method, a triangle wedge of the fundus at the angle of His is excised by using a linear stapler to divide the stomach from the apex of the fundus to the dilator about 2 or 3 cm from the gastroesophageal junction. Another stapler is passed from the apex of the first staple line to the angle of His. When the stapler is fired, the neoesophagus is created. The fundus is then used for the fundoplication (Fig. 23-19).

Laparoscopic and Open Toupet Fundoplication. Abdominal access for a Toupet fundoplication is similar to a Nissen fundoplication with respect to patient positioning and port placement. This is a 270-degree posterior fundoplication. The initial steps of the procedure are similar to a Nissen fundoplication for mobilization of the esophagus and repair of the hiatal hernia. The fundus is passed posterior to the esophagus in similar manner, but rather than a 360-degree wrap, each end of the fundoplication is sutured to the left and right anterolateral aspects of the esophagus with two interrupted nonabsorbable sutures for a 270-degree wrap (Fig. 23-20). To secure the wrap, the posterior gastric fundus is sutured to the right and left crus. As in the Nissen fundoplication, care must be taken to avoid injury to the anterior vagal trunk while suturing the fundus to the esophagus. This procedure is often employed in patients with esophageal motility disorders such as achalasia to prevent an outlet obstruction at the gastroesophageal junction.

**FIGURE 23-20** A completed Toupet fundoplication.

**FAILURE RATES AND REOPERATION**
Failure rates for fundoplication have been reported to range from 2% to 17% for laparoscopic procedures to 9% to 30% for the open approach.\textsuperscript{86,92,93} However, the overall reoperation rate after laparoscopic fundoplication is approximately 5%.\textsuperscript{94–97} In a large retrospective database study of 13,000 patients over 15 years in the United States, reoperation most commonly occurred within the first year after initial surgery (1.7%), with a steady decline to 4 years, after which time it remained constant at approximately 0.5% per year.\textsuperscript{98}

While initial antireflux operations have been shown to have the best chance at success, advances in surgical technique have allowed for improving results in redo surgery. Up to 84% of patients undergoing initial reoperation will have a good result.\textsuperscript{92} Important principles of reoperative antireflux procedures include comprehensive reevaluation by objective testing (upper endoscopy, contrast esophagogram, manometry, pH monitoring, MII-pH, and gastric emptying studies) to properly identify the etiology of symptoms, complete reversal of any previous fundoplication to identify the natural anatomy, preservation of vagal nerves, identification of short esophagus, and proper approximation of the posterior crura prior to performing the new fundoplication. Redo antireflux surgery can be performed laparoscopically with excellent results.\textsuperscript{94,99}

Nevertheless, patients who have undergone a redo fundoplication are at risk of yet another failure. Depending on operative findings, attempt at redo fundoplication may be appropriate. However, depending on findings of anatomic and physiologic testing, after the second or third redo fundoplication has failed, consideration should be given to resection. If esophageal function is adequate but gastric function poor, a total gastrectomy with long Roux-en-Y esophagojejunostomy may be appropriate. If esophageal function is poor, consideration for an esophagectomy may be appropriate.

**Endoluminal Therapy**

Recently, there have been attempts to develop endoluminal treatments for GERD. These have centered on either endoscopic construction of a “valve” at the gastroesophageal junction or “augmentation” of the LES. It is beyond the scope of this chapter to provide a comprehensive review of these techniques.
and devices, as many are now off the market. Nevertheless, we discuss two that are still commercially available and have data to support their use.

**ENDOLUMINAL RADIOFREQUENCY APPLICATION**

Radiofrequency application involves a catheter that is passed orally into the distal esophagus. The balloon is expanded and electrodes pierce into the esophageal submucosa. Radiofrequency energy is delivered. The subsequent tissue reaction results in contraction of the distal esophagus, “augmenting” the LES (Fig. 23-21). This approach has resulted in improvements in symptoms and objective measures of GERD, but the mechanism by which it works is poorly understood. While results across trials have been conflicting, a meta-analysis of trials comparing radiofrequency ablation (Stretta™ system, Mederi Therapeutics, Inc., Norwalk, CT) with sham therapy and PPI for patients with GERD was found not to produce significant changes in physiologic and other parameters, including time spent at a pH less than 4, lower esophageal sphincter pressure, ability to stop PPIs, or health-related QoL.
Few studies have investigated the long-term safety of this procedure, but those that have report a low mortality rate (<0.1%) and low overall morbidity (0.2%-8.6%), with superficial mucosal injury (2.5%-8.3%), transient postprocedure chest pain (1.7%-58%), and transient dysphagia (0.8%-8.3%) being most common. Esophageal stricture, while seemingly possible, has not been reported in large follow-up studies.\textsuperscript{101–103} Although the device is still commercially available, its routine use remains controversial.

**TRANSORAL INCISIONLESS FUNDOPPLICATION**

Transoral incisionless fundoplication (TIF) was first described in 2008,\textsuperscript{103a} and the EsophyX\textsuperscript{®} device (EndoGastricSolutions, Inc., Redmond, WA) was FDA-cleared in 2007 (CE marked 2006). The TIF technique creates a “neogastroesophageal valve” (Fig. 23-22). The procedure was designed to create serosa-to-serosa plications, including the muscle layers, to construct valves 270-300 degrees in circumference and 3 cm long by deploying multiple nonabsorbable polypropylene fasteners through the esophageal and gastric layers in a circumferential pattern around the GEJ.\textsuperscript{104–106} A randomized trial of TIF versus omeprazole reported TIF was an effective treatment for patients with GERD symptoms, particularly in those with persistent regurgitation despite PPI therapy,\textsuperscript{106a} based on evaluation 6 months after the procedure.\textsuperscript{107}
Principles of Postoperative Care and Adverse Outcomes

Although there is some variation in practice with respect to postoperative care of patients having undergone antireflux surgery, certain principles need to be followed. Increased intra-abdominal pressure associated with nausea and vomiting should be aggressively avoided in the early postoperative period to prevent mechanical disruption of the fundoplication. Some surgeons routinely place a nasogastric tube at the end of the operation and use antiemetics liberally. Although some will perform an esophagogram with water-soluble contrast postoperatively to assess for fundoplication position and to rule out occult perforation, this is not mandatory. If an initial trial of liquid intake is undertaken without dysphagia, patients may be started on a soft diet as early as postoperative day 1. Typical postoperative hospital stay is 1 to 4 days, but patients are generally maintained on a soft diet for 2 to 6 weeks before being transitioned to a regular diet as tolerated. Some degree of postoperative dysphagia is common in the early period due to edema within the wrap, and patients should be reassured that in most cases dysphagia will resolve within 3 months. In up to 10% of cases, however, dysphagia persists.
longer than 3 months, and the etiology should be investigated. Most cases of persistent postoperative dysphagia have some mechanical cause, such as transthoracic migration of the fundoplication, tight crural closure, or poor construction of the wrap, requiring reoperation.\textsuperscript{108}

Intraoperative and early complications include esophageal and gastric perforation (<2%), pneumothorax, splenic injury, bleeding, and visceral injury. Mortality rates range from 0.008\% to 0.8\% while morbidity is also very low, at 2\%.\textsuperscript{109} The most common side effects of laparoscopic Nissen fundoplication are bloating, diarrhea, and dysphagia.\textsuperscript{110} Of patients undergoing laparoscopic antireflux surgery, only 2\% to 6\% will eventually require reoperation. Of those, the majority are due to transthoracic herniation of the repair (10\%-60\%), with “slipped” fundoplications making up the majority of the remaining cases (15\%-30\%). Other reported indications for reoperation include tight fundoplication, missed motility disorder, and paraesophageal hernia.\textsuperscript{111} Of those requiring reoperation, close to three-quarters will present within the first 2 years after initial operation.\textsuperscript{112}

### PARAESOPHAGEAL HERNIAS

#### Definition and Classification

Hiatal hernias are herniation of the stomach or other abdominal organs into the chest through the esophageal hiatus in the diaphragm. There are traditionally four types of hiatal hernias. Type I is defined as a migration of the GEJ into the chest secondary to an attenuated phrenoesophageal ligament. The “sliding” (type I) hernia and is the most common type of hiatal hernia. True paraesophageal hernias (PEH), or type II hiatal hernias, occur when the gastric fundus herniates anterior to the esophagus while the GEJ remains in the abdomen. Type III hiatal hernias are a combination of types I and II, in which both the GEJ and the gastric fundus herniate into the chest. Type IV hiatal hernias occur when not only the stomach, but other abdominal organs such as the colon, also herniates into the chest through the esophageal hiatus (\textit{Fig. 23-23}). Of note, PEH (types II-IV) account for only about 14\% of all hiatal hernias, with about 90\% of all PEH being of the type III variety.\textsuperscript{113}
Presentation

Patients with PEH can present with a variable set of symptoms, which can range from asymptomatic to life threatening. Symptoms of reflux such as heartburn are present in the majority of these patients. Other symptoms specifically associated with the anatomic location of the stomach after herniation through the hiatus into the chest can include dysphagia, postprandial bloating, nausea, vomiting, and even respiratory compromise.\(^{114}\)

One important but less obvious symptom of PEH is chronic anemia. Anemia results from the development of Cameron’s erosions or (ulcers) within the gastric folds secondary to repetitive movement through the esophageal hiatus. Cameron’s erosions occur where the stomach slides over hiatal crura. At this region, the pressure of the stomach on the crura leads to ischemia of the gastric mucosa. More than one-third of patients with PEH can have an associated anemia, with about 60% having resolution after PEH repair.\(^{115}\)

The life-threatening complication of PEH is gastric volvulus, which can lead to incarceration and subsequent strangulation. This is caused by abnormal rotation of the stomach >180 degrees along one of two axes, creating a closed-loop obstruction. The first and most common type occurs when the stomach rotates along an imaginary line connecting the GEJ and the
pylorus, referred to as organoaxial rotation. The second type, mesoaxial rotation, occurs when the stomach rotates about an imaginary line between the greater and lesser curvatures. Of these, organoaxial volvulus is associated with a higher incidence of strangulation and is more often associated with PEH. The classic symptoms associated with gastric volvulus are known as Borchardt’s triad and include epigastric pain, nonproductive retching, and inability to pass a nasogastric tube. However, true strangulation of the stomach in a paraesophageal hernia is very rare.

**Evaluation**

Evaluation begins with a history and physical examination, as PEH can have nonspecific symptoms which may be attributable to other pathology. Both contrast upper gastrointestinal (UGI) series and esophagogastroduodenoscopy (EGD) are implemented in assessing the extent and severity of PEH. The UGI study allows for visualization of the size of the hiatal defect, the amount of stomach herniated into the mediastinum, gastric volvulus, and presence of obstruction (Fig. 23-24). EGD is used to assess the presence of other esophageal/gastric pathology, such as a tumor, gastric bleeding, ulceration, and mucosal ischemia, suggestive of strangulation. Routine pH-monitoring or esophageal motility studies on patients with PEH are not necessary. However, in cases where dysphagia is a primary symptom, esophageal manometry is useful to assess for other motility disorders. In cases where reflux symptoms are the primary presenting symptoms, pH monitoring can confirm pathologic GERD as the cause, thereby better predicting surgical outcome.
Management

Management decisions in patients with PEH can be complex. Generally, this is an older age group with multiple comorbidities. Patients with symptomatic PEH who are acceptable operative risk should be offered surgical repair, as it will improve symptoms and QoL.\textsuperscript{117} Traditionally, all patients with PEH have been offered repair because of concern about life-threatening complications.\textsuperscript{118} Recently, however, analysis of potential outcomes of asymptomatic or minimally symptomatic PEH patients concluded that after considering operative risk and surgical benefit to patients, watchful waiting would be more beneficial than elective PEH repair in approximately 83% of
Therefore, a thorough assessment of symptoms and risks should drive the decision to operate.

**Operative Repair**

While PEHs have traditionally been repaired through either a laparotomy or thoracotomy, today it is generally accepted that laparoscopy is the preferred method of repair. As this technique has evolved, laparoscopic repair is feasible in most patients.

The patient is placed in the lithotomy position as with a standard laparoscopic antireflux operation. Attention is first turned toward the hernia sac, which is easily identified (Fig. 23-25). No attempt at reduction of the herniated stomach or other organs should be made, as stomach is attached to the hernia sac and traction on the stomach could lead to organ injury. The hernia sac is divided along the left crus to enter the plane between the hernia sac and mediastinum (Fig. 23-26). This is a critical step, as unlike other hernia sacs, the hernia sac of a PEH has two layers: the peritoneum and the phrenoesophageal ligament. The hernia sac can then be bluntly dissected from the mediastinum in a relatively bloodless plane between the hernia sac and pleura (Fig. 23-27). As the hernia sac is dissected from the mediastinum, the hernia contents will naturally come with it. Care needs to be exercised, as the hernia sac will overlie the esophagus (Fig. 23-28). Not uncommonly, the hernia sac may extend posterior to the esophagus. This portion must also be dissected and excised to allow for adequate visualization of the retroesophageal space. Once the hernia sac is reduced, it may be resected to improve visualization. The esophagus is encircled with a Penrose drain and the right and left crura exposed (Fig. 23-29). The hiatal defect is repaired as previously described. The large defect can be problematic because of tension.
FIGURE 23-25 Laparoscopic identification of the paraesophageal hernia.
FIGURE 23-26  Beginning the dissection of the paraesophageal hernia sac.

FIGURE 23-27  The proper plane between the hernia sac and pleura.
FIGURE 23-28  Identification of esophagus as the hernia sac is reduced.
Adjuncts have been used to reinforce this repair. They include the use of a variety of biologic and prosthetic meshes and relaxing incisions. No adjunctive techniques have definitively led to reduction in hernia recurrence. However, crural repair with prosthetic mesh has been associated with complications such as erosion into the esophagus or stomach, dysphagia, and pain. If esophageal foreshortening is encountered, a lengthening procedure such as a Collis gastroplasty can be performed.

Another controversy in PEH repair is the need for an antireflux procedure. Some patients who have undergone PEH repair without a fundoplication will have symptomatic improvement of their PEH; however, new symptoms of GERD may develop. Therefore, unless there is a specific contraindication to an antireflux procedure, most patients would benefit from a Nissen or Toupet fundoplication in addition to the hiatal hernia repair.
Finally, another technique that has been utilized in an effort to prevent recurrence is gastropexy/gastrostomy. The stomach can be anchored to the abdominal wall via these techniques. No proven benefit has been shown to date with any fixation of the stomach in the abdominal cavity, but some studies have shown relatively good outcomes. Therefore, gastropexy can be considered a surgeon’s preference, rather than a mandated principle.

BARRETTE ESOPHAGUS

Barrett esophagus (BE) is a change in the mucosa of the esophagus from squamous epithelium to metaplasia columnar epithelium as a result of GERD. The clinical significance of BE is its role as a risk factor in the development of esophageal adenocarcinoma (EA). Patients with BE are up to 40 times more likely to develop esophageal adenocarcinoma than the general population. Prior to 40 years ago, BE was not a significant clinical problem because EA made up a small minority of esophageal cancers and cancers overall. However, the incidence of EA has increased since the late 1970s in the Western world, most likely related to GERD and subsequent BE.

Pathogenesis

Barrett metaplasia occurs as a result of exposure of esophageal epithelium to gastric and duodenal fluids. When native squamous esophageal mucosa is exposed to gastric acid and duodenal bile, it undergoes an adaptive metaplasia to become mucus-secreting columnar cells with interspersed goblet cells. Following metaplasia, these cells can then undergo morphologic changes called dysplasia. Pathologically, dysplastic cells tend to be distorted and crowded. Furthermore, these cells have nuclear abnormalities, including increased nuclear to cytoplasmic ratios. Based on pathologic appearance, dysplasia can be described as low grade (LGD), high grade (HGD), intermediate, or indeterminate (Fig. 23-30). At the genetic level, cells that have undergone Barrett metaplasia also demonstrate many properties of carcinogenesis including growth self-sufficiency, inhibition of antigrowth signals, escape from apoptosis, limitless replication, angiogenesis, invasion, and metastasis.
FIGURE 23-30  Histologic grades of Barrett esophagus.

Diagnosis

The typical patients with BE tend to be overweight, middle-aged white men with symptoms of reflux.\textsuperscript{131} However, many patients can have “silent” reflux and can still have BE despite being completely asymptomatic. Only an upper endoscopy can confirm the diagnosis. Upon examination, BE is grossly appreciated as salmon-colored mucosa projecting proximally into the distal esophagus from the normal squamocolumnar junction (Fig. 23-31A). Endoscopic use of narrow-band imaging can enhance visualization of the BE (Fig. 23-31B). These suspicious areas must be biopsied to confirm the presence of intestinal metaplasia and goblet cells.\textsuperscript{132} Endoscopic biopsy must be done using the Seattle protocol of four quadrant biopsies every 2 cm or less from the anatomic gastroesophageal junction. The extent of the endoscopic BE is described using the Prague classification system of length of circumferential BE (C) and total length of esophagus involving with the BE (M). For example, if the circumferential length involved was 3 cm and a “tongue” of BE extended an additional 2 cm cephalad, this would be reported as C3M5. Special note must be made of nodules and ulcers. These should be biopsied thoroughly.

**Screening**

Many groups have advocated screening patients considered high-risk for developing BE and subsequent EA. Some retrospectively designed studies have demonstrated benefits of screening certain patient populations, but there is no level I evidence demonstrating an improvement in survival as a result of endoscopic screening. As cost is an issue with screening programs, groups have developed models to show that it is cost-effective to screen those patients deemed to be at high risk. However, identifying the “high-risk” patient can be problematic and there is no consensus as to what makes a patient high-risk. Because of this, screening recommendations remain controversial. At this time, the American College of Gastroenterology does not recommend routine screening for BE or EA, but the British Society of Gastroenterology states that it is acceptable to screen patients with chronic GERD and other risk factors including age >50 years, white race, male sex, and obesity.

**Surveillance**

After BE has been diagnosed, surveillance recommendations depend on the presence and degree of dysplasia present. Surveillance of nondysplastic BE (NDBE) remains the most controversial. Some suggest that surveillance is not required, as 97% of NDBE patients will be cancer-free in 10 years. However, others argue that a progression to cancer rate of 0.4% to 0.6% per year justifies surveillance. If no dysplasia is found by pathologic examination on the index endoscopy, then the patient should undergo repeat endoscopy with biopsies within 1 year. If this confirms NDBE, surveillance can be extended to every 3 to 5 years. If LGD is found, it should be confirmed by an expert gastroenterologic pathologist. Patients with LGD should continue to undergo surveillance annually until they have two consecutive dysplasia-free biopsies. Finally, if HGD is found on biopsy, it must again be confirmed by an expert gastroenterologic pathologist. If ablation is not done, then intense surveillance should be implemented for
HGD including repeat endoscopy with biopsies within 3 months (Fig. 23-32).

**FIGURE 23-32** Algorithm of surveillance for Barrett esophagus.

**Treatment of BE**

The management of patients with BE is based upon the degree of dysplasia. The initial treatment strategy for all patients with BE should be geared at the treatment of reflux. PPI therapy is the mainstay in the management of BE. Acid-suppressing medications can lead to a 71% reduction in cases of EA and/or HGD transformation in patients with BE.\(^{138}\) Although once a day or twice a day dosing is controversial, compliance with daily PPI is mandatory.

**ENDOSCOPIC ABLATION OF BARRETT ESOPHAGUS**

There have been many techniques introduced to ablate BE in hopes of reducing EA risk. At one time, photodynamic therapy was widely used. However, it was associated with issues related to “buried glands” and severe stricture formation. Because of this, it has fallen out of favor and is not discussed in this chapter. Other techniques, such a thermal
electrocoagulation, argon beam coagulation, and laser ablation have led to inconsistent results. Therefore, these are not part of the mainstay of treatment. The best studied techniques are radiofrequency ablation and, to a far lesser extent, cryoablation.

**Indications**

**Nondysplastic Barrett Esophagus.** The incidence of progression to EA in patients with NDBE is about 4 to 6 per 1000 patients per year. Ablation of NDBE is controversial, but some have advocated ablation for specific reasons. At present, the consensus statement from the American Gastroenterological Association does not recommend the “routine” ablation of NDBE. However, ablation can be considered in the “high-risk” patient for the progression to EA with NDBE. Risk factors to consider are a family history of EA, long BE length, difficult-to-control reflux, or patient preference.

**Low-Grade Dysplasia.** The incidence of progression to EA in patients with LGD is about 7 to 8 per 1000 patients per year. As with NDBE, this has led to a recommendation against ablation. However, a recent randomized controlled trial demonstrated unequivocally that ablation reduces the incidence of progression to EA. Given these new results, ablation of LGD may be considered appropriate.

**High-Grade Dysplasia.** There is complete consensus that HGD should be ablated. The incidence to progression to EA is about 14 to 15 per 1000 patients per year. A randomized controlled trial demonstrated significant reduction in the risk to progression to EA with ablation.

**Techniques of Endoscopic Ablation**

**Radiofrequency Ablation.** Radiofrequency ablation (RFA) is the best studied of the ablative techniques. The device used most commonly is the BARRx™ system (Fig. 23-33; Covidien, Sunnyvale, CA). In this method, a complete upper endoscopy is done and the length of BE to be treated is determined. Circumferential BE is treated with the Halo-360 device, while “spot” ablative devices, such as the Halo-90, can be used for smaller areas. If the Halo-360 is used, the esophageal mucosa is cleared of any debride and a guidewire passed
into the stomach. A sizing balloon catheter is passed over the guidewire to the level to be treated. The balloon is inflated and the appropriate size ablation catheter chosen. An ablation catheter is passed over the guidewire and the endoscope passed alongside the ablation catheter. The top of the ablation coils are positioned cephalad to the top edge of the BE. The ablation balloon is inflated, suction applied to the endoscope, and the device activated. It delivers 10 Joules of energy. The ablation balloon is deflated, the coagulum is removed from the surface of the esophagus, and the process is repeated. This process is continued until the length of BE desired to be treated is ablated (Fig. 23-34). If one of the spot devices is used, this is done under direct visualization with the device either attached to the endoscope or through the endoscope. Complications such as chest pain, esophageal strictureing, and hemorrhage have been reported, but these complications are quite uncommon.142

**FIGURE 23-33** BARRx System for radiofrequency ablation of Barrett esophagus. (All rights reserved. Used with the permission of Medtronic.)
Cryotherapy. Cryotherapy causes mucosal destruction through repeated freeze-thaw cycles using agents such as liquid nitrogen. The technique utilizes a catheter passed through the endoscope. Liquid nitrogen at $-70^\circ C$ is applied under direct visualization to the area of BE to be ablated. A retrospective study has demonstrated that 97% of patients treated with cryotherapy had eradication of their HGD, 87% had eradication of all dysplasia, and 57% had eradication of their BE altogether.\textsuperscript{143} This study revealed a few treatment-related complications, including chest pain and strictures. However, there have been no randomized trials documenting the effectiveness of cryoablation.
Combining Ablation of BE with Antireflux Surgery. The risk of recurrence of BE after ablation is related to persistent reflux. Because of this, it is reasonable to consider antireflux surgery, especially in the symptomatic patient. This has led to a decrease in the recurrence of BE after successful ablation.

Endoscopic Mucosal Resection. The endoscopic counterpart to ablative therapy is endoscopic resection. This is achieved either via endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). EMR is a technique that involves resecting both the mucosa and submucosa of an area of interest using snare cautery similar to how polypectomies are performed in the colon. The advantage of these techniques compared to ablative modalities is that they provide tissue specimens that can be sent to pathology for accurate staging. Because of the ability to obtain a pathologic specimen, EMR or ESD is the primary treatment of nodular BE, especially HGD, as nodules are more likely to harbor malignancy. EMR is the mucosal resection technique employed most frequently in the United States and Europe. This can be preceded by submucosal elevation of the lesion using a combination of saline and epinephrine if need be. A band similar to one used for variceal bleeding is placed at the base of the nodule after it is sucked into the banding cap. This creates a “pseudopolyp” that can be resected with a snare in a similar fashion to an endoscopic polypectomy. When patients with dysplasia and early-stage EA are treated with EMR, complete local remission rates range from 91% to 96%. A drawback of EMR is that its use is restricted to lesions that are less than 15 mm. EMR can be combined with RFA of the remaining flat BE.

With larger lesions, the advanced technique of ESD can be used. This technique uses endoscopic electrosurgical knives rather than a snare to resect the specimen en bloc. Complications seen in these procedures include bleeding, perforation, and stricturing, but mortalities are rare.

ESOPHAGECTOMY

Occasionally, BE will require an esophagectomy. Indications include BE nodules harboring a T1b (tumor invades submucosa) or greater EA, persistent BE with HGD despite multiple attempts at ablation, complicated strictures or ulcers intractable to conservative management, and the “burnt-out”
esophagus which leads to functional obstruction. Although esophagectomy is consider elsewhere in this book, consideration should be given to creation of a fundoplication with the esophagectomy to reduce the symptoms of reflux and the incidence of BE after an esophagectomy (Fig. 23-35).150


**CONCLUSION**

GERD is a commonly encountered medical problem, especially in the Western world. The importance of this condition and proper evaluation, treatment, and surveillance is highlighted by its potentially devastating complications, namely BE and EA. Physicians should have a high index of suspicion when evaluating patients, as GERD can present with varying clinical pictures. Diagnostic technology is continually advancing, and a comprehensive workup should be implemented in all suspected cases of GERD. Treatment options can range from lifestyle modification to open surgery, and varies on a case-by-case basis. The hope is that with the advent
of newer, less invasive treatment modalities such as endoluminal and laparoscopic interventions, efficacy will continue to improve while morbidity rates will decline.

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Paraesophageal hernias comprise approximately 5% to 15% of all hiatal hernias and are challenging hernias to repair. Most commonly, these occur in patients age >50 to 60 years. The natural history of paraesophageal hernia repair has not been systematically studied, but, in general, many patients present with a longstanding history of hiatal hernia. Therefore, it’s likely that these progressively enlarge over time. While they can be asymptomatic, some patients present with acute gastric outlet obstruction and/or gastric ischemia that requires emergency surgical intervention. In this chapter, the clinical presentation, diagnostic evaluation, and surgical technical aspects and resultant outcomes of paraesophageal hernia repair will be presented.

**BACKGROUND**

The classification of hiatal hernia is illustrated by the radiographic studies shown in Figure 24-1. Type I hernias are sliding hiatal hernias defined by the location of the gastroesophageal (GE) junction above the diaphragm. Types II, III, and IV are different types of paraesophageal hernias. In type II paraesophageal hernias (PEHs), the GE junction is in a normal position and a
portion of the upper stomach, usually the fundus, is herniated alongside the esophagus through the hiatus. Type II PEHs account for a relatively small percentage of cases. The most common type of PEH is type III, in which there is a combined sliding and paraesophageal component. These hernias can be quite large, with most of the stomach, if not the entire stomach, in the chest and associated volvulus. Type IV PEHs are those in which some other organ besides the stomach is herniated into the chest, most commonly the colon, but also possibly the small bowel, pancreas, and duodenum.
FIGURE 24-1 Barium swallow that illustrates the 4 types of hiatal hernias.  
A. Type I sliding hernia.  B. Type II paraesophageal hernia (PEH).  C. Type III PEH.  D. Type IV PEH with intrathoracic stomach; note the bowel gas in the left chest, which is due to herniated colon.

Because of the large size of the defect and extent of herniation, the stomach may undergo rotation within the hernia sac. Most commonly, this consists of organoaxial volvulus in which the stomach rotates along the axis of the organ. This type of volvulus results in the greater curvature being flipped upward and at a higher position in the mediastinum than the lesser curvature (Fig. 24-2A). The stomach can also rotate along the axis of its mesentery (mesoaxial volvulus). Mesoaxial volvulus is associated with a higher risk of gastric ischemia because of the twisting of the mesentery, which can compromise venous return and gastric blood flow (Fig. 24-2B).
FIGURE 24-2  A. Barium swallow that shows organoaxial volvulus. Note that the stomach is essentially upside down, with the greater curvature of the stomach positioned higher than the lesser curvature. B. Barium swallow that shows a PEH with mesoaxial volvulus.

CLINICAL PRESENTATION

Patients with PEH may be completely asymptomatic, but more often, they have a variety of symptoms depending on the extent of the herniation. There may be a longstanding history of hiatal hernia that has been managed medically. Postprandial fullness, discomfort, and pain, especially after eating a larger meal, are some of the most common symptoms associated with PEH. These symptoms occur because the herniated segment does not empty properly, and therefore, with a larger meal, the stomach becomes distended, which leads to discomfort. Typical heartburn and regurgitation symptoms of gastroesophageal reflux disease (GERD) may be present but are less common, likely because these patients may still have a competent lower esophageal sphincter. Patients may also have dysphagia either because of associated esophageal dysmotility or because the large hernia compresses the distal esophagus. Approximately 25% of patients present with anemia from gastrointestinal bleeding. The bleeding is usually occult and discovered incidentally on a routine blood count. Anemia in this setting is typically due to Cameron lesions, which are superficial erosions or ulcerations in the proximal stomach that can be secondary to constriction of the stomach at the hiatal defect and friction from movement across the hiatus, which can lead to occult blood loss. PEH may also be detected incidentally on plain chest radiographs as shown in Figure 24-3 or on computed tomography (CT) scan done for chest pain or other reasons (Fig. 24-4).
FIGURE 24-3 Chest radiograph in a patient with a large paraesophageal hernia. Note the air fluid level in the chest from the herniated stomach.
FIGURE 24-4  Computed tomography scan that demonstrates a large paraesophageal hernia: (A) axial images and (B) coronal view. The fluid-
filled stomach is seen on the coronal view and colonic gas along with stomach on the axial image.

Up to 20% of patients with PEH present with gastric volvulus. While gastric volvulus can be asymptomatic, it can also develop acutely and lead to gastric outlet obstruction with acute onset of chest or epigastric pain, nausea, and emesis. In some cases, the volvulus may lead to gastric ischemia and strangulation. Most patients who present with acute gastric outlet obstruction can be temporized with nasogastric decompression. However, some patients require emergency surgery to reduce the stomach and avoid progression to gastric strangulation. Inability to pass a nasogastric tube should raise concern for gastric volvulus with possible gastric ischemia.

**DIAGNOSTIC EVALUATION**

The diagnosis and evaluation of a patient with a PEH typically involve a multistep process and numerous tests once the diagnosis is suspected. When the diagnosis is suspected, the initial evaluation should consist of a barium esophagram and esophagogastroduodenoscopy (EGD). The barium swallow may be useful in defining the anatomy, the type of hiatal hernia, and in particular, the relationship of the GE junction to the diaphragm. If the GE junction is located more than 5 cm above the hiatus, then the patient may have a shortened esophagus (Fig. 24-5). This is a very useful initial test as it typically yields a significant amount of information about the anatomy and function of the esophagus and stomach.
FIGURE 24-5  Barium swallow in a patient with a shortened esophagus. The gastroesophageal junction is not well visualized but was more than 5 cm above the hiatus, and at operation, an esophageal lengthening procedure was performed.

Further diagnostic evaluation should be carried out that consists of an upper gastrointestinal endoscopy to assess for mucosal lesions and other upper gastrointestinal pathology including the presence of Cameron ulcers and to evaluate the stomach. Factors evaluated at the time of EGD include the
size of the hernia, which is often appreciated with retroflexed view. In acute presentations, an EGD can be used to assess the viability of stomach if there is concern for ischemia.

Because patients with PEH may have associated esophageal dysmotility or hypomotility from longstanding reflux and the large hernia, high-resolution esophageal manometry is advisable for most patients to identify this condition and for selection of the proper type of fundoplication to be done at the time of repair. In some cases, it may be difficult for the manometry catheter to pass through the GE junction and assess the lower esophageal sphincter, which can be compressed by the herniated contents. In general, a 24-hour pH test is not indicated for PEH because the presence of the hernia is sufficient objective evidence of the underlying pathology and the results do not typically alter the surgical approach.

OPERATIVE APPROACH

PEH repair can be challenging for a number of reasons, including the large amount of herniated contents, the presence of a large hiatal defect that must be closed, need to excise a large hernia sac, the possibility of a shortened esophagus, and often distorted anatomy. In addition, these patients are frequently older with more comorbidities and accompanying obesity, which can increase the difficulty and risks of surgical repair.

PEHs may be repaired either via an open abdominal, open thoracic, or laparoscopic transabdominal approach. Over the past 20 years, laparoscopic PEH repair has largely replaced these other approaches except in the rare, unstable patient who does not tolerate a pneumoperitoneum or the septic patient with gastric necrosis. The operation may be segmented into 3 primary steps, the details of which are provided in Table 24-1: (1) dissection and reduction of the hernia sac and stomach into the abdomen; (2) closure of the crural/hiatal defect; and (3) creation of the fundoplication. Patient preparation should consist of a single dose of intravenous antibiotic (first-generation cephalosporin unless allergic), lower leg compression devices and subcutaneous heparin for thromboembolic prophylaxis, and placement of a urinary catheter. The patient is typically positioned on a bean bag mattress that is well padded and with the legs on spreader bars so the surgeon can stand between the legs.
TABLE 24-1: SEQUENTIAL STEPS IN PARAESOPHAGEAL HERNIA REPAIR

Step 1: Dissection of hernia sac and reduction of herniated contents
• Division of gastrohepatic ligament
• Incision of phrenoesophageal ligament and development of sac plane
• Division of phrenoesophageal and hernia sac attachments to crura
• Exposure of base of crura from right side
• Division of gastroplenic ligament
• Completion of retroesophageal window
• Complete reduction of sac and herniated contents into abdomen
• Circumferential mobilization of esophagus in mediastinum with identification and preservation of vagal nerve trunks
• Excision of hernia sac
• Decision regarding adequacy of esophageal length
• If short esophagus present, perform wedge fundectomy to lengthen esophagus with 54- to 60-Fr bougie dilator in place

Step 2: Closure of the hiatal defect
• Crural closure starting posteriorly with interrupted nonabsorbable suture ± pledgets
• Placement of bioresorbable mesh to reinforce hiatal closure if indicated according to surgeon judgment

Step 3: Creation of fundoplication
• Complete Nissen fundoplication; short floppy wrap over distal esophagus
• Partial fundoplication if inadequate peristalsis or contraction reserve is present
• Perform gastropexy if deemed necessary

Step 1. Dissection of the Hernia Sac and Reduction of the Herniated Contents

At initial laparoscopic exploration, one may attempt to reduce the herniated contents, but this is often difficult to achieve without first dissecting the hernia sac (Fig. 24-6). One should use gentle traction and avoid forcible reduction because of the risk of tearing or perforating the stomach. An
advanced energy device (most commonly an ultrasonic coagulator) facilitates dissection of the hernia sac and mobilization of the upper stomach and esophagus. The dissection can begin either on the anatomic right or left side of the stomach. The authors prefer to begin by dividing the gastrohepatic ligament up to the right crus of the diaphragm. The hepatic branch of the vagus nerve can be divided, but one should take care to identify (and preserve) a replaced left hepatic artery, which can be present in up to 30% of cases. The phrenoesophageal membrane and edge of the hernia sac are then incised anteriorly, and the plane between the sac and the mediastinum should be developed and then extended toward the right and left crura (Fig. 24-7). This maneuver is critical for beginning to reduce contents out of the mediastinum and can largely be done by blunt dissection. The dissection of the sac continues along the right side down to the base of the crura and into the retroesophageal space until the left crus has been identified. It is important to preserve the thin fascial layer over the crura, which provides strength for the subsequent crural closure. Once the right side has been freed up and the retroesophageal window started, the left anterior phrenoesophageal and gastrophrenic attachments can be divided, which allows one to begin to reduce the sac out of the left side of the mediastinum. At this point, it is often preferable to open the gastroepiploic omentum beginning at the level of the upper body of the stomach and dividing it up to the left crus, taking the short gastric vessels with an ultrasonic coagulator (Fig. 24-8). With large PEHs, the short gastric pedicle is often elongated, which can make this step in the operation easier than with conventional hiatal hernia repair. The short gastrics should be taken close to the stomach to avoid injury near their entry into the spleen, which can be difficult to control, and also to avoid leaving redundant tissue on the fundus for the subsequent fundoplication. The attachments at the base of the left crus are then divided, and at this point, one should visualize a completed retroesophageal window (Fig. 24-9).
FIGURE 24-6 Initial laparoscopic view of a large paraesophageal hernia.
FIGURE 24-7  Incision of the paraesophageal hernia sac. This step is typically done with use of an advanced energy device (eg, ultrasonic coagulator) but also by blunt dissection within the sac plane.
FIGURE 24-8 Division of the gastrosplenic ligament and short gastric vessels, which is typically done with an ultrasonic coagulator or other advanced energy device.

FIGURE 24-9 Completed retroesophageal window with visualization of the right and left crura and aorta. A, aorta; E, esophagus; IVC, inferior vena cava;
LC, left crus; RC, right crus.

Next, the dissection is carried back into the mediastinum where the esophagus is mobilized circumferentially, taking care to identify and preserve both anterior and vagal nerve trunks, which can be distorted in their location by the large hernia (Fig. 24-10). Retraction on the esophagus and upper stomach during mediastinal mobilization can be accomplished either by placing a grasper in the retroesophageal window or by a Penrose drain placed around the esophagus at the hiatus.

**FIGURE 24-10** Mediastinal dissection with view of the posterior vagus nerve (arrow).

It is often helpful at this point to excise the hernia sac, which is usually larger on the left anterior side (Fig. 24-11). The hernia sac may serve as a lead point for possible hernia recurrence, and in some small studies, excision of the hernia sac has been associated with a reduced hernia recurrence rate.²
FIGURE 24-11  Excision of the hernia sac on the left anterior side of the stomach. It is important to maintain traction and countertraction on the sac and stomach and to identify and avoid injury to the anterior vagus nerve, which can be in close juxtaposition to the medial edge of the sac and to the stomach itself.

When excising the sac, one must be careful to avoid injuring the anterior vagus nerve, which can be closely applied to the base of the sac. In some cases, there is also redundant sac to excise on the anatomic right side, and care should be taken there to identify and preserve the posterior vagus nerve during that step.

Once the contents are completely reduced and the esophagus has been extensively mobilized, a determination should be made as to whether or not there is adequate intra-abdominal length of 2.5 to 3 cm or more. If not, then an esophagogastric lengthening procedure may need to be performed, as described below. Other precautions include the importance of proper traction and countertraction to expose the relevant anatomy at each stage in the operation. One should also be careful with the use of energy near the
esophagus, stomach, and vagus nerves because of the risk of direct thermal spread to those structures.

**Step 2: Closure of the Hiatal Defect**

Once the hernia has been reduced and the esophagus has been fully mobilized, the hiatal defect should be repaired. The crura should be closed with interrupted nonabsorbable sutures, preferably 0 polyester-type sutures (Fig. 24-12). The closure should begin posteriorly with either simple interrupted or figure of 8 sutures or a combination thereof. Some surgeons prefer to use pledgeted sutures to buttress the closure. If mesh is to be used, it should be placed at this step in the operation. It may be necessary with larger defects to also place a crural closure stitch anterior to the esophagus because of increasing tension posteriorly. In cases in which there is a wide defect that cannot be closed primarily, a relaxing incision can be made in the right crus to bring the crura together at the midline. This defect from the relaxing incision would then need to be covered with some type of mesh, as will be discussed below.
**Step 3: Creation of Fundoplication**

After the hiatal defect has been closed, a fundoplication should be carried out and is typically done over a large, 54- to 60-Fr bougie dilator. The wrap should be located over the distal esophagus (or in the case of esophageal lengthening, over the neoesophagus). A short, floppy wrap of 3 sutures of interrupted 0 polyester is carried out with 1 or 2 of these sutures incorporating a bite of the esophageal wall to prevent the wrap from slipping (Fig. 24-13A). Pledgets should generally be avoided in the fundoplication because of the risk of fistulization. Upon completion of the fundoplication, one should be able to easily slide a blunt instrument beneath the wrap and alongside the esophagus. A gastropexy anchoring the posterior fundus to the diaphragm or the anterior stomach to the abdominal wall can be carried out, but there is no consensus on whether this impacts recurrence rates or not. For patients who have aperistalsis or profound hypomotility or inadequate contraction reserve on high-resolution manometry, a partial fundoplication should be performed (Fig. 24-13B). Typically, a posterior Toupet fundoplication is done, but some surgeons prefer an anterior Dor fundoplication instead.
Placement of Mesh

The use of mesh for the repair of large PEHs is an area of controversy that is unresolved. The one consensus among surgeons is that the use of permanent synthetic mesh at the hiatus should generally be avoided due to the rare but catastrophic risk of mesh erosion into the esophagus, which may require treatment with esophagectomy.\(^3\text{-}^6\) The use of biologic mesh gained considerable interest after the initial results of a randomized trial in 2006.\(^7\) In this prospective, randomized trial, the authors compared hiatal reinforcement with biologic mesh (4-ply, porcine, small intestine submucosa) to primary hiatal closure only in 108 patients. At the 6-month radiographic follow-up, they found a significant reduction in the rate of recurrent hernia (24% vs 9%) in patients who underwent mesh reinforcement. However, when a subgroup of 60 of these patients was followed out to 5 years, the beneficial effect of biologic mesh reinforcement was lost, with recurrent hernia rates of 59% in the primary repair group versus 54% in the reinforced group.\(^8\) A limitation of the long-term data of this study was that a substantial portion of the patient population was lost to follow-up. Despite the high anatomic recurrence rate in both groups, symptoms were significantly improved in the vast majority of cases, and only 2 patients (3%) required reoperation. Regardless, based on this and other studies, the current recommendation on the use of mesh reinforcement at the time of PEH repair is that it appears to reduce short-term recurrence rates but may not impact long-term recurrence outcomes. In a European consensus panel review on PEH management, a majority of experts felt that the use of mesh was important under specific circumstances such as large hiatal defect and the quality of the crura; there was no consensus, however, on the type of mesh that should be used.\(^9\) Further studies with later generation biologic or other bioresorbable mesh options are needed before a definitive recommendation can be made.

In regard to the choice of biologic or bioresorbable mesh, a variety of materials are available for use, as illustrated in Figure 24-14. In general, biologic meshes should be employed to buttress the primary crural closure.
and not to bridge the crural defect because the material resorbs over time. Numerous fixation techniques have been used, including sutures, tacks, and glues.\textsuperscript{10,11} Regardless of the method, great care should be taken to avoid injury to the pericardium or aorta when using penetrating fixation options, which has been reported during PEH repair.\textsuperscript{12-14}
FIGURE 24-14  Examples of biologic mesh used for hiatal reinforcement of the crural closure in PEH repair. A. Acellular porcine dermis. B. Porcine small intestine submucosa. C. Synthetic polyglycolic acid and trimethylene carbonate resorbable mesh. Note the combination of resorbable tacks and permanent suture (2-0 polyester) used to fixate the mesh.

Use of Relaxing Incisions

During the repair of large hiatal hernias or when there is excessive tension on the hiatus during closure, it may be necessary to use a crural relaxing incision to reduce the radial tension and allow closure at the hiatal defect. The right crus may be especially thin and begin to tear during closure of very large, wide defects. While relaxing incisions can be performed on either the right or left crus, it is usually easier in the authors’ experience to do this on the right side along the lines indicated in using an ultrasonic coagulator. The incision should be placed laterally near the inferior vena cava, preserving a cuff of crus that can be used to suture the mesh in place, and should extend more anteriorly, where tension is greater, than posteriorly. On the left side, the relaxing incision should start to the left of the hiatus and follow the course of the seventh rib. In a more recent study, Bradley et al\textsuperscript{15} demonstrated that the addition of a left crus relaxing incision reduced tension by 35.8%, whereas a right crural relaxing incision reduced tension by 46.2%.\textsuperscript{15} When combining both methods, the tension was reduced by 56.1%.

Most authors recommend covering the defect of the relaxing incision with a bioresorbable mesh. Short-term studies have shown acceptable results with the use of crural relaxing incisions when combined with biologic mesh reinforcement.\textsuperscript{16,17} However, the use of biologic mesh for relaxing incisions in the left crus was associated with subsequent development of diaphragmatic hernias in one report.\textsuperscript{18} Further long-term studies are needed to validate the success of this approach.

Esophageal Lengthening

Most surgeons agree that adequate esophageal length is crucial for reducing the risk of hernia recurrence. With extensive mediastinal esophageal dissection, the goal is to bring the GE junction at least 3 cm into the abdomen
without tension. When the appropriate amount of esophageal length cannot be obtained by additional esophageal mediastinal dissection, the addition of an esophageal lengthening procedure should be considered. In the classic Collis gastroplasty, a linear stapler is fired alongside the esophagus onto the stomach at the angle of His to create a neoesophagus of 3 cm or more in length. This maneuver is difficult to perform laparoscopically, however, because of the angle of the stapler, and so more often, a wedge resection of the fundus is done (as shown in Fig. 24-15). The wedge resection may require 2 or more applications of an articulating 6-cm stapler (blue cartridge load) and should always be done with a 54-Fr or larger bougie dilator in the esophagus to avoid narrowing of the GE junction. The stapler is maximally flexed and then first fired down across the top of the fundus toward the bougie. In some cases, a second load must be fired to get divide the fundus to the side of the bougie. The final staple load is fired cephalad, adjacent to the bougie alongside the GE junction. The staple line should then be incorporated into the fundoplication to minimize the risk of a leak.
FIGURE 24-15 Collis gastroplasty technique using a wedge resection of the gastric fundus. A. With a 54-Fr bougie dilator in place, a 60-cm linear stapler is fired across the upper fundus toward the bougie. B. Second firing across the stomach to reach the bougie dilator in the proximal stomach. C. The stapler is then oriented angling cephalad alongside the bougie and fired to complete the wedge excision. D. The completed wedge resection line with an additional 3 cm of length added and creation of the “neoesophagus.”

A technical issue that should be considered when deciding to include a Collis gastroplasty is that the neoesophagus does not exhibit normal esophageal peristaltic actions, which may result in potential dysphagia. In one study of 171 GERD patients, a short esophagus that required a Collis gastroplasty was found in 6.4% of patients. During a mean follow-up of 43
months, good symptom control was achieved in all patients and no reherniations were observed. Another study found good long-term symptomatic outcomes in 52 patients who underwent Collis gastroplasty during hiatal hernia repair by either open transthoracic or laparoscopic approaches.

Addition of an Antireflux Procedure

The addition of a fundoplication has become standard in the repair of PEHs. The reason for this is that even if the patient did not have reflux preoperatively, the extensive mobilization and division of the phrenicoesophageal ligaments may predispose to reflux postoperatively, which has been demonstrated in up to 30% of patients after PEH repair with no prior history of GERD. In addition, the fundoplication may help anchor the upper stomach intra-abdominally. Recently, a small, prospective, randomized trial was reported in which 40 patients were randomized during PEH repair using a mesh augmented hiatal repair to receive either fundoplication or a simple cardiophrenicopexy. At the 12-month follow-up, reflux scores were lower in the fundoplication group, and esophagitis was present endoscopically in 54% of the cardiophrenicopexy patients versus 17% of patients who had a fundoplication. DeMeester scores were also significantly lower in the fundoplication group at 3 months. These findings further support routine fundoplication in PEH repair.

Other Considerations

EMERGENCY PEH REPAIR

A small percentage of patients with PEH may present acutely with symptoms of obstruction and possible strangulation. In one decision analysis model, the likelihood of developing acute symptoms that required emergency surgery was estimated to be 1.16% annually, and the lifetime risk of acute symptomatic presentation from the age of 65 at diagnosis onward was 18%. The majority of patients who present acutely are clinically stable and can be managed by decompression with a nasogastric tube and subsequent elective surgery after a complete diagnostic evaluation has been done. In a study of
the National Surgical Quality Improvement Program (NSQIP) database of 3498 patients with PEH, only 5% required emergent surgery.\textsuperscript{29} Emergency surgery has also been associated with an increased rate of morbidity and higher mortality, even when controlled for patient age and comorbidities, and is more often done in an open fashion.\textsuperscript{29-32}

Emergent surgery for PEH is a challenging procedure and, therefore, should be carried out in high-volume centers if possible, which may also reduce the need for emergency surgery.\textsuperscript{33} Most emergent cases can be done laparoscopically but require considerable experience due to the increased difficulty of managing an incarcerated, edematous stomach. If a patient cannot be decompressed by a nasogastric tube, then urgent endoscopic decompression can be attempted provided the patient is stable and does not have signs of ischemia. The indications for emergent surgical intervention include evidence of peritonitis or gastric perforation, inability to decompress the stomach by nasogastric tube or endoscopically, or suspicion of gastric ischemia (markedly elevated white blood cell count, concerning findings on CT scan, bloody emesis or nasogastric drainage, or ischemic endoscopic appearance). The operative steps are similar as for elective PEH repair. However, if the stomach cannot be reduced laparoscopically or if there is gastric necrosis, the operation should be converted to an open procedure via an upper midline incision.

**ELDERLY PATIENTS**

An additional consideration in PEH repair is that many of the patients are elderly, which may impact recovery and outcomes. In one study that analyzed outcomes by age group, patients age 75 years and older had similar symptomatic outcomes to those under age 75 and without an increase in morbidity.\textsuperscript{34} In another study of patients with giant PEH age 70 and older (median age, 78 years), the major morbidity rate after repair was 15.5\% and repair resulted in significant symptomatic improvement.\textsuperscript{35} Of note, 13\% of patients in this series presented acutely and required urgent repair. Finally, an analysis of the NSQIP database identified 313 patients age 80 and older who underwent PEH repair. The analysis found that mortality and serious morbidity were not different between patients ≥80 years old versus those under age 80.\textsuperscript{36} These results suggest that laparoscopic PEH repair can be safely performed in elderly patients without increased risk.
GASTROSTOMY TUBE PLACEMENT

In patients with numerous underlying medical comorbidities who may not be candidates for definitive surgical repair, other techniques have been described that may reduce the patient’s symptoms. The use of a percutaneous endoscopic gastrostomy (PEG) tube or laparoscopically placed G-tube has been advocated for some patients as a method to reduce the stomach and secure it within the abdominal cavity in patients who are too frail to undergo definitive surgery. Alternatively, this method can also be used to temporize patients before definitive surgical repair, although that is rarely indicated.

OUTCOMES

Laparoscopic PEH repair has been shown to be effective in controlling symptoms despite a high rate of recurrent hiatal hernia radiographically. These results appear similar to those seen with open PEH repair in terms of hernia recurrence rates. A summary of selected laparoscopic series with long-term follow-up and outcomes is shown in Table 24-2. In the majority of series, recurrent hernias were seen in 20% to 35% of cases. However, the rate of observed recurrence also depends on whether radiographic evaluation was done, which detects more recurrences than if based on symptoms alone. Recurrences also appear to increase over time and, in one series, went from 16% at 1 year to 39% at 5 or more years of follow-up. In Dallemagne’s series of 85 patients with 10-year follow-up, the observed recurrence rate was 65%; in the prospective, randomized trial carried out by Oelschlager, the radiographic recurrence rate was over 50%, both in the primary repair and biologic mesh groups. Most series have shown that patients with recurrences are more likely to have symptoms than those who do not have a recurrent hernia. Despite these findings, the rate of reoperation has been low (<5%) in the majority of reported series.

TABLE 24-2: SELECTED SERIES OF OUTCOMES OF LAPAROSCOPIC PARAESOPHAGEAL HERNIA REPAIR WITH LONG-TERM FOLLOW-UP
As noted earlier, the role of mesh in repair of large hiatal hernias and PEHs is controversial. In the Oelschlager-led prospective, randomized trial that compared primary closure versus buttress with porcine small intestinal submucosa, the radiographic recurrence rate at 6 months was 24% in the primary closure group versus 9% in the biologic mesh group.\(^7\) However, at 5-year radiographic follow-up in a subset of patients, the recurrence rates were 59% in the primary repair group and 54% in the biology mesh group.\(^8\) A similar trial using 4-ply porcine small intestine submucosa and titanized polypropylene mesh that compared suture repair versus absorbable mesh versus nonabsorbable mesh showed recurrence rates of 23.1%, 30.8%, and 12.8%, respectively, at the 1-year follow-up.\(^48\) Four systematic reviews and meta-analyses have analyzed this topic over the past 4 years, the results of which are shown in Table 24-3.\(^49-52\) The number of studies and patients included varied in these reports, but overall appeared to favor mesh for a reduction in the rate of recurrent hiatal hernia. In the analysis by Memon and colleagues,\(^51\) mesh placement was associated with a lower rate of reoperation but did not impact hernia recurrence rate or incidence of wrap migration. These findings suggest that the use of mesh for PEH repair should be individualized according to the local conditions at the hiatus and surgical expertise with the use of mesh in this location.

### Table 24-3: Results of Systematic Review and Meta-Analyses of Mesh Repair for Large Hiatal Hernias

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Patients</th>
<th>Mean Age (years)</th>
<th>Recurrences</th>
<th>Reoperation</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gangopadhyay 2006</td>
<td>171</td>
<td>65</td>
<td>40 (23.7%)</td>
<td>1 (0.6%)</td>
<td>25.3 months</td>
</tr>
<tr>
<td>White 2008</td>
<td>31</td>
<td>63</td>
<td>10 (52%)</td>
<td>2 (6.5%)</td>
<td>11.3 years</td>
</tr>
<tr>
<td>Lukeich 2010</td>
<td>662</td>
<td>70</td>
<td>70/445 (15.7%)</td>
<td>21 (3.2%)</td>
<td>22 months*</td>
</tr>
<tr>
<td>Furnee 2010</td>
<td>70</td>
<td>60.6</td>
<td>18 (30%)</td>
<td>8 (11.4%)</td>
<td>45.6 months</td>
</tr>
<tr>
<td>Dallemagne 2011</td>
<td>85</td>
<td>66</td>
<td>23 (65%)</td>
<td>2 (3%)</td>
<td>39 months</td>
</tr>
<tr>
<td>Mittal 2011(^b)</td>
<td>73</td>
<td>70.6</td>
<td>4 (5.5%)</td>
<td>1 (1.4%)</td>
<td>1-5 years</td>
</tr>
<tr>
<td>Taragarona 2013</td>
<td>77</td>
<td>64</td>
<td>20/46 (46%)</td>
<td>3 (3.9%)</td>
<td>107 months</td>
</tr>
<tr>
<td>Jones 2015</td>
<td>209</td>
<td>57.6</td>
<td>35/166 (21%)</td>
<td>1 (0.6%)</td>
<td>25 months</td>
</tr>
<tr>
<td>Lidor 2015</td>
<td>111</td>
<td>61</td>
<td>19 (28%)(^c)</td>
<td>4 (3.6%)</td>
<td>43.5 months</td>
</tr>
<tr>
<td>Wang 2015</td>
<td>115</td>
<td>64</td>
<td>41 (35.7%)</td>
<td>2 (1.7%)</td>
<td>5 years</td>
</tr>
</tbody>
</table>

\(^1\)Represents median age and follow-up.
\(^2\)Patients all had intrathoracic stomach defined as >75% stomach in the chest with associated organooxial volvulus. Only 36 patients had follow-up beyond 1 year.
\(^3\)Recurrence rate based on 70 patients who underwent radiographic evaluation at 1 year.

**MESH SERIES**

As noted earlier, the role of mesh in repair of large hiatal hernias and PEHs is controversial. In the Oelschlager-led prospective, randomized trial that compared primary closure versus buttress with porcine small intestinal submucosa, the radiographic recurrence rate at 6 months was 24% in the primary closure group versus 9% in the biologic mesh group.\(^7\) However, at 5-year radiographic follow-up in a subset of patients, the recurrence rates were 59% in the primary repair group and 54% in the biology mesh group.\(^8\) A similar trial using 4-ply porcine small intestine submucosa and titanized polypropylene mesh that compared suture repair versus absorbable mesh versus nonabsorbable mesh showed recurrence rates of 23.1%, 30.8%, and 12.8%, respectively, at the 1-year follow-up.\(^48\) Four systematic reviews and meta-analyses have analyzed this topic over the past 4 years, the results of which are shown in Table 24-3.\(^49-52\) The number of studies and patients included varied in these reports, but overall appeared to favor mesh for a reduction in the rate of recurrent hiatal hernia. In the analysis by Memon and colleagues,\(^51\) mesh placement was associated with a lower rate of reoperation but did not impact hernia recurrence rate or incidence of wrap migration. These findings suggest that the use of mesh for PEH repair should be individualized according to the local conditions at the hiatus and surgical expertise with the use of mesh in this location.
Complications associated with PEH repair are those common to any foregut operation. These include gastric or esophageal perforation, bleeding, acute re herniation, and esophageal outflow obstruction, as well as general risks of thromboembolic, cardiac, and other complications. Perforation of the esophagus or stomach may result from excessive traction during the dissection, thermal injury to the esophagus or stomach, esophageal lengthening procedures, or insertion of a bougie dilator for calibration of the fundoplication. In an analysis of 379 patients who underwent primary PEH repair, the intraoperative perforation rate was 1.8%, and the most common mechanism was retraction injury to the stomach.\textsuperscript{53} If a perforation occurs, it should be repaired with a 2-layer sutured closure, and a radiographic swallow should be obtained the following day. One must be careful to avoid contact of advanced energy devices (eg, ultrasonic coagulator) with the esophagus or stomach during or immediately after activation to avoid a thermal injury to the esophagus, stomach, or vagus nerves. The esophagus may be especially at risk of thermal injury because of the absence of a serosal layer.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Studies</th>
<th>Type of Analysis</th>
<th>No. of Patients</th>
<th>Recurrence Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furnee</td>
<td>26</td>
<td>Suture vs mesh</td>
<td>Suture: 247</td>
<td>Suture: 26.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mesh: 451</td>
<td>Me: 15.6%</td>
</tr>
<tr>
<td>Huddy</td>
<td>9</td>
<td>Suture vs synthetic vs biologic mesh</td>
<td>Suture: 310</td>
<td>Suture: 24.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Synthetic mesh: 214</td>
<td>Synthetic mesh: 12.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biologic mesh: 152</td>
<td>Biologic mesh: 17.1%</td>
</tr>
<tr>
<td>Memon</td>
<td>4</td>
<td>Suture vs mesh</td>
<td>Suture: 186</td>
<td>Not reported</td>
</tr>
<tr>
<td>2016\textsuperscript{a}</td>
<td></td>
<td></td>
<td>Mesh: 220</td>
<td></td>
</tr>
<tr>
<td>Tam</td>
<td>13</td>
<td>Suture vs mesh</td>
<td>Suture: 382</td>
<td>Suture: 24%</td>
</tr>
<tr>
<td>2016\textsuperscript{b}</td>
<td></td>
<td></td>
<td>Mesh: 354</td>
<td>Mesh: 13%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Analysis favored mesh placement for reoperation rate only, but not for recurrence rate and wrap migration.

\textsuperscript{b}Analysis favored mesh placement for recurrence rate but not reoperation rate.
Delayed esophageal perforation may also occur at the staple line following an esophageal lengthening procedure. This complication can often be managed by endoscopic clipping or stenting of the site of perforation. Nutrition can be delivered by either intravenous total parenteral nutrition or by feeding tube placement until healing has occurred. For patients who present with a leak postoperatively, if there are signs of peritonitis, mediastinitis, or sepsis, then emergent surgical exploration and drainage are indicated. If the leak is primarily into the chest and mediastinum, then a thoracotomy will likely be required for management.

Intraoperative bleeding most often results from injury to the spleen or splenic vessels. The best strategy is prevention by staying close to the stomach during dissection and division of the short gastric vessels, and avoiding excessive traction on the spleen. Minor splenic capsule injuries can often be controlled with tamponade and topical hemostatics. Major splenic bleeding should be managed by splenectomy. Another potential source of major and catastrophic hemorrhage during PEH repair is the aorta. Special care should be taken when dissecting posteriorly in the mediastinum, and one should avoid sweeping movements toward the aorta with the ultrasonic coagulator or scissors tips. One should also avoid placement of tacks (during mesh placement) in the hiatus in the vicinity of the aorta or deep sutures placed at the base of the crura. Cardiac tamponade has also been reported from tack placement anteriorly where the heart lies across the diaphragm.12-14

Acute reherniation of the wrap through the hiatus may occur in the immediate postoperative period, although this is uncommon. Most often, this occurrence is associated with an acute diaphragmatic stress event such as postoperative retching and emesis. For this reason, it has been our practice to administer routine emetics postoperatively to patients for the first day to minimize this risk. One should also be aware of the potential for acute reherniation in the operating room during emergence from anesthesia as the patient reacts to the endotracheal tube, which can result in vigorous Valsalva contractions with transfer of forces to the hiatus.

Esophageal outflow obstruction with symptomatic dysphagia may occur immediately after surgery or in a delayed fashion. Most commonly, this is due to obstruction at the fundoplication but can also be due to a tight crural closure or an underlying esophageal motility disorder that was not recognized preoperatively. Patients who are unable to tolerate clear liquids or who fail to empty their esophagus in the immediate postoperative period should be
evaluated by barium swallow and should be considered for early revision of the fundoplication (Fig. 24-16). For those who present in a delayed fashion, endoscopic dilation should be considered, which may provide sufficient relief of symptoms. Symptomatic dysphagia can also be a manifestation of recurrent hiatal hernia and is one of the primary reasons for reoperation after PEH repair.

![Acute esophageal outflow obstruction in a patient on postoperative day 1 following paraesophageal hernia repair and Nissen fundoplication. Minimal contrast passes through a narrowed gastroesophageal junction, and the esophagus is dilated proximally. This required a return to the operating room and conversion to a partial fundoplication.](image)

**FIGURE 24-16** Acute esophageal outflow obstruction in a patient on postoperative day 1 following paraesophageal hernia repair and Nissen fundoplication. Minimal contrast passes through a narrowed gastroesophageal junction, and the esophagus is dilated proximally. This required a return to the operating room and conversion to a partial fundoplication.

**RECURRENCES AND REOPERATIVE**
CONSIDERATIONS

Despite the relatively high rate of recurrent hiatal hernia that can be seen after PEH repair, most patients are either asymptomatic or have symptoms that can be managed medically. This observation may be in part because a patient with a large PEH has been converted to a small type I recurrence. For this reason, most surgeons will defer reoperation on patients unless they have symptoms that cannot be managed medically. In addition, patients may also develop a recurrent PEH in the setting of prior laparoscopic antireflux surgery and repair of a type I hiatal hernia years previously (Fig. 24-17). When evaluating patients with symptomatic recurrence, the preoperative evaluation should include a barium esophagram to assess the anatomy, an EGD to assess for the nature of the recurrence and any strictures or mucosal lesions (Fig. 24-18), and high-resolution manometry. Twenty-four-hour pH testing is not usually necessary unless the symptoms are atypical. In addition, it is advisable to obtain and review any previous operative report(s) to determine the type of repair and fundoplication that was performed previously and whether any mesh was used, which may influence the operative planning.
Repair of recurrent PEHs should be carried out by surgeons with extensive experience in foregut surgery because these are challenging operations due to the extensive scarring at the hiatus. In experienced centers, outcomes after reoperation may be similar to first-time PEH repair despite longer operative times and a higher rate of use of a Collis gastroplasty and temporary gastrostomy tubes. Although initial port placement and operative approach are the same as for a first-time operation, often the left lateral section of the liver will be adherent to the lesser omentum, stomach, and diaphragmatic crus and must be freed to gain exposure to the hiatus and allow for retraction of the liver. Much of the dissection can be done with a laparoscopic Metzenbaum-type scissors using both sharp and blunt dissection techniques with minimal use of energy. All attachments at the hiatus should be freed and the esophagus mobilized within the mediastinum to the greatest extent possible. A determination should be made as to the mechanism of the recurrence (ie, whether it is due to failure at the hiatal closure, a short esophagus, or other technical and patient-related factors). It is generally recommended that any previous fundoplication be taken down completely at the time of the surgery to facilitate exposing the left and right crura and to allow the surgeon to have a full understanding of the anatomy and adequacy
of esophageal length. It is also more likely that additional techniques such as mesh reinforcement of the hiatal closure and the need for an esophageal lengthening procedure will be necessary to complete the repair and reduce the risk of subsequent recurrence.

The risk of esophageal or gastric perforation is increased in patients who undergo redo hiatal hernia repair and, in reported series, has been approximately 14%. In most cases, these injuries can be repaired laparoscopically. It has been our practice to obtain a radiographic water-soluble contrast swallow study the morning after any redo PEH repair to exclude a leak and assess for esophageal emptying and anatomy.

**POSTOPERATIVE MANAGEMENT**

Postoperatively, patients are usually started on clear liquids the morning after surgery and advanced to an esophageal diet as tolerated. Dietary instruction should be provided by a dietician before discharge. For patients who have undergone a difficult repair or redo surgery or if esophageal lengthening has been performed, a water-soluble contrast is done the morning after surgery prior to initiation of oral intake. Acid suppression medication is stopped unless the patient has undergone esophageal lengthening or had active esophagitis preoperatively. Most patients can be discharged between 1 and 3 days postoperatively depending on their age, medical comorbidities, and recovery status. After discharge, the diet may be liberalized after 2 to 3 weeks provided the patient is having no swallowing issues. Patients should be counseled about minimizing any major diaphragmatic stress long-term such as maintaining a healthy weight and avoiding severe coughing or emesis. Our practice has been to discharge patients with a prescription for an antiemetic in the event that they develop nausea. Follow-up should occur within 3 to 4 weeks. Our patients are seen subsequently at 1 year unless symptoms dictate sooner follow-up, at which time a barium swallow is obtained to document the anatomic integrity of the repair. Symptomatic assessment with a validated instrument such as the GERD Health-Related Quality of Life scale can be useful for monitoring and comparing symptoms prior to surgery and during follow-up.

**SUMMARY**
Laparoscopic PEH repair is a challenging operation that has good symptomatic outcomes as reported in high-volume centers. The foundational principles of management include a thorough preoperative diagnostic evaluation, careful risk assessment for surgery, and precise surgical technique with dissection and reduction of the hernia sac, primary crural closure with or without biologic mesh reinforcement of the hiatus, and creation of a fundoplication tailored to the patient’s esophageal motility. Surgeons who undertake these operations should also be prepared for the possibility of a shortened esophagus and need for a crural relaxing incision to achieve hiatal closure. Further advancements are needed to reduce the rate of radiographic recurrences after PEH repair.

REFERENCES


This chapter is written by experts in the surgical treatment of a wide variety of benign esophagogastric diseases, and presents a comprehensive picture of how to manage these patients. In this commentary, we discuss indications for operation, the surgical skill required, and the techniques required to address these benign conditions.

WHAT’S SO BENIGN ABOUT BENIGN ESOPHAGEAL DISEASES?

There is a funny thing about digestive diseases, at least when it comes to their surgical treatment (perhaps their medical treatment as well—another subject….): that is that, in the universal scales of the gods of health, there seems to be an equal “disease burden” between benign and functional
diseases and cancer. This balance extends from anal/rectal disease (rectal cancer vs sphincter dysfunction, condylomata, hemorrhoids, etc), colon (colon cancer vs inflammatory bowel disease [IBD], irritable bowel syndrome [IBS], constipation, volvulus etc), small bowel (cancer vs IBD, bleeding small bowel obstruction [SBO]), Hepato-pancreato-biliary (HPB) (bilio/duodenal/pancreatic cancer vs ulcer, pancreatitis, etc.), gastric (gastric cancer vs gastroparesis, peptic ulcer disease [PUD], dyspepsia, bleeding, etc.) and esophageal (cancer vs motility disorders, achalasia, gastroesophageal reflux disease [GERD], hiatal hernia, non-cardiac chest pain, dysphagia, etc.). Obviously gastrointestinal (GI) cancer is not a good thing, and rightfully deserves a lot of attention. However, GI cancers are relatively rare when compared to functional and benign diseases. Furthermore, benign functional digestive diseases have been shown to often have a quality of life impact comparable to the worst chronic medical conditions such as diabetes, but also to debilitating acute problems such as trauma and cancer.\textsuperscript{1–4} With IBD as a possible exception, the medical world, industry, and the public spends more time, money, and human resources on GI cancers than it does on the far more prevalent, costly, and often equally debilitating chronic/functional benign conditions. Of course, digestive cancers kill the majority of patients, and other than from narcotic drug overdose, the benign diseases seldom lead to death.

\textbf{IS SURGERY THE BEST OPTION FOR PATIENTS WITH BENIGN OR FUNCTIONAL FOREGUT DISEASE?}

All of the conditions addressed in this section have a surgical option. It may be a radical surgery, minimally invasive, or endoscopic, but at some point some of these benign and essentially medical problems will need some sort of surgery. This is a daunting decision point: “…at some point, some of these, and some sort of surgery…” should give any sensible surgeon pause. For the surgeon and the patient with a benign foregut issue, particularly for the more chronic or functional diagnoses, the proper answer to these questions is essential. In general, a conservative initial approach is a good idea for most conditions. For the more functional conditions—noncardiac chest pain, dysphagia, gastroparetic symptoms, etc.—extensive attempts to treat
conservatively is mandatory before proceeding to surgery. This is because there is a substantial risk that surgery will not improve the patient’s symptoms—and can even make them worse. For benign disease with a more objective definition or anatomic state, such as GERD, achalasia, and paraesophageal hernia (PEH), medical attempts at symptom control are less important but still might be required by third-party payers and offer a reassurance to the patient that the discomforts, costs, and side effects of the surgery were worth it.

BENIGN FOREGUT SURGERY AS AN ARTFORM

A major problem with many benign foregut procedures is that they are reconstructive, and optimal techniques are not well described. In addition, there is a wide variety of patient anatomy, physiology, and psychology to which to adapt the surgery. Mistakes in this realm can lead to severely unhappy patients even in the face of objectively good results. The other major problem with these surgeries is that “mastery” necessitates a holistic interest in the patient and therefore has a substantially long learning curve to achieve this highest degree of ability. Antireflux surgery provides a good example of this. In spite of being around since the 1950s, there remain a plethora of described surgical variations, both global (partial vs total fundoplication) and particular (construction with or without a bougie? etc.). Even in the face of level one evidence of the superiority or equivalency of technical approaches or details, practitioners will continue to argue and advocate their own “brand” of functional repair. In the end, it is probably more the experience of the practitioner that will determine the quality of the outcome more than particular technical details. This is one reason that education in benign foregut operations is of critical importance, and probably justifies postgraduate fellowship training. Training for true mastery, in our opinion, should cover all aspects of the disease; diagnostics, endoscopy, minimally invasive surgery, open surgery, complication management, etc. rather than just the technical aspects of the operations.
WORKUP

A common element of all benign digestive diseases being considered for surgical treatments is the need for comprehensive evaluation before crafting a surgical plan. This can include imaging, and almost always will include endoscopy. Optimally, the endoscopy should be performed by the surgeons themselves, as it is an excellent way to understand the personalized anatomy and evaluate the extent and severity of the patient’s pathology. A fairly unique aspect of benign foregut disease is the interconnectedness of many of these functional disorders: diverticuli are often associated with spastic motility disorders, as is noncardiac chest pain; gastroparesis can be expressed by GERD symptoms, achalasia frequently presents as heartburn/reflux, and so forth. Because of this, comprehensive evaluation and testing is needed to achieve a total picture of the disease state and allow a treatment plan to be developed that addresses all aspects leading up to the presenting complaint. Nothing is more disappointing to the patient than having residual or new symptoms after a procedure for a benign issue. The important takeaway then is to be thorough—even redundant—in preoperative testing, and to address all discovered issues at the time of surgery.

ARTISTIC TECHNIQUE

Many procedures for benign foregut disease, particularly antireflux surgery, suffer from wide variations in quality of outcomes. By and large, this is a result of either poor patient selection, inappropriate procedure choice, or technically poor procedure performance. These procedures, as opposed to extirpative or ablative procedures, attempt to restore or establish function of a rather complex and not totally understood part of the digestive tract. Consider all of the controversy that continues to exist regarding the physiology of the LES: Is it related to a decreased sphincter pressure or anatomic configuration of a flap valve? Where exactly does it start and stop in relation to external or internal landmarks? What is the contribution of the crura? How does hiatal hernia play into its function? And so forth. The same is true for many of the other benign diseases of the foregut—achalasia, peptic ulcer disease, gastroparesis, spastic disorders, and diverticula. These are all rather vague as to what constitutes “normal” and how exactly to get there surgically. This combination of a poor understanding of how things work and mediocre
landmarks for how to get there leads to poorly proscribed surgical recipes for reconstructive surgery. This explains why, many decades after first being described, there are many named techniques to perform antireflux or achalasia surgery (Nissen, Dor, Toupet, Hill, Lind, Watson, etc.) and even more variations within the named procedures. Such a diversity shows that these surgeries are more of a philosophic reflection or art form than a well-defined repair. The problem with this, of course, is that it makes teaching and learning these operations very difficult, and attaining mastery requires a particular focus on the disease and patient as well as many years of practice, and this knowledge may not be easily transferred to the next generation.

COMPREHENSIVE FOLLOW-UP

Operations for benign diseases have a particular need for follow-up after surgery. This is primarily related to the subjective nature of their presenting symptoms and the frequent disconnect between subjective perception of symptoms after surgery and objective test results. It has been well documented for reflux diseases, achalasia, and gastroparesis that almost 50% of postoperative patients complaining of symptoms such as heartburn, dysphagia, and delayed gastric emptying in fact have completely normal studies.\(^7\),\(^8\) And conversely, many patients with a perfect subjective result after functional restorative surgery will have abnormal results. Our philosophy, in the face of this disconnection, is to strongly urge all postoperative patients with benign reconstructive surgery to have objective testing at some point after the operation. Table 25-1 lists our current follow-up recommendations for a variety of benign diseases.

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**TABLE 25-1: FOLLOW-UP PARADIGMS**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Early (&lt;3 mo)</th>
<th>6 mo</th>
<th>12 mo</th>
<th>3 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>SX</td>
<td>SX</td>
<td>SX, Mano, 24 hr pH</td>
<td>SX</td>
<td>SX, EGD</td>
</tr>
<tr>
<td>PEH</td>
<td>SX</td>
<td>SX, UGI</td>
<td>Mano, 24-hr pH, EGD</td>
<td>SX</td>
<td>SX, UGI</td>
</tr>
<tr>
<td>Achalasia</td>
<td>SX</td>
<td>SX, TBS, Mano, pH, EGD</td>
<td>SX</td>
<td>TBS</td>
<td>SX, EGD, 24-hr pH, TBS</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>SX</td>
<td>SX, EGD, GES</td>
<td>SX</td>
<td>GES</td>
<td>SX</td>
</tr>
<tr>
<td>PUD</td>
<td>SX</td>
<td>SX, EGD</td>
<td>SX</td>
<td>0</td>
<td>SX, EGD</td>
</tr>
<tr>
<td>Esophageal diverticula</td>
<td>SX</td>
<td>SX, UGI</td>
<td>EGD, 24-hr pH</td>
<td>0</td>
<td>SX, UGI</td>
</tr>
<tr>
<td>Submucosal tumor</td>
<td>0</td>
<td>EGD</td>
<td>0</td>
<td>0</td>
<td>EGD</td>
</tr>
</tbody>
</table>

Abbreviations: SX, symptom score/quality of life; Mano, manometry; 24-hr pH, 24-hour pH test; EGD, esophagogastroduodenoscopy; UGI, upper GI barium swallow; TBS, timed barium swallow; GES, gastric emptying study; PEH, paraesophageal hernia; PUD, peptic ulcer disease.
CONCLUSION

Benign indications for surgery of the foregut represent a disease burden equal to if not greater than malignant indications. The highly subjective spectrum of presentation, the need for an artist-like approach to restoration of functional anatomy, and the unpredictable nature of symptomatic results make surgery for these indications somewhat daunting and frustrating. The surgeon’s tools in this treatment are thorough evaluation and objective follow-up, meticulous technique, and the knowledge that great experience brings.

REFERENCES

HISTORY

Historically, surgery is the mainstay of treatment for esophageal cancer. Czerny was the first who resected a cervical esophageal cancer in 1877. In 1913, Torek performed the first transthoracic esophageal cancer resection successfully. A rubber tube was used as the esophageal substitute connecting the esophagostomy and gastrostomy for feeding in the patient, who lived for another 17 years. Reconstruction using stomach as a conduit after intrathoracic esophageal cancer resection was performed by Ohsawa, a Japanese surgeon in Kyoto, in 1933. In 1946, Lewis described a 2-phase approach via right thoracotomy and laparotomy. Tanner reported the same procedure in 1947. McKeown later described the 3-phase esophagectomy via right thoracotomy, laparotomy, and cervical incision.

In addition to surgical treatment, there has been a proliferation of treatment options, especially with regard to different combinations of chemotherapeutic agents and radiotherapy, in the past 2 decades. Significant divergence in the epidemiologic pattern between Western and Eastern
countries has been observed, which has had a major impact on the management of this disease.

**EPIDEMIOLOGY**

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer.\(^6\) There is significant variation of incidence among different geographic regions and various ethnic groups. The disease is common in countries of the so-called “Asian esophageal cancer belt,” which stretches from eastern Turkey and east of Caspian Sea through northern Iran, northern Afghanistan, and southern areas of the former Soviet Union, such as Turkmenistan, Uzbekistan, and Tajikistan, to northern China and India. In high incidence areas, the occurrence of esophageal cancer is 50- to 100-fold higher than that in the rest of the world. It is the fourth most common cancer in China.\(^7\) The age-standardized incidence rate of esophageal cancer in China is 27.4 per 100,000, compared to 10 in Japan, 7.9 in northern Europe, 7.6 in western Europe, 5.8 in North America, and 5.5 in Australia/New Zealand.\(^6\) The crude age-adjusted mortality is up to 140 per 100,000, and esophageal cancer is the one of the most common causes of cancer death in China.\(^8\) Esophageal cancer most commonly presents in the sixth and seventh decades of life. In most countries, esophageal cancer is a male-predominant disease.

Over the past three decades, there has been an epidemiologic shift from squamous cell cancers to adenocarcinoma of the lower esophagus and cardia in the white populations in Western countries. The incidence of adenocarcinoma has surpassed that of squamous cell cancers since the 1990s. In Eastern countries, however, squamous cell cancer remains the predominant type and is mostly located in the mid esophagus.

**ETIOLOGY**

The etiologic factors for the development of esophageal cancer vary between the different histologies (Table 26-1). Smoking and drinking are independent contributing factors, as shown by prospective studies of patient who drink but do not smoke and, conversely, of patients who smoke but do not drink.\(^9\)
TABLE 26-1: ETIOLOGIC FACTORS OF ESOPHAGEAL CANCER

<table>
<thead>
<tr>
<th>Factor</th>
<th>Squamous Cell Cancer</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Hot beverages</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>N-nitroso–containing food</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>(eg. pickled vegetables)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewing betel nut</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Mate drinking</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Deficiencies of fresh green</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>vegetables, fruits, and vitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low socioeconomic class</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Fungal toxin or virus</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>History of radiation to</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>mediastinum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lye corrosive stricture</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>History of aerodigestive</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plummer-Vinson syndrome</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Achalasia</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Obesity</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Barrett esophagus</td>
<td>−</td>
<td>+++</td>
</tr>
</tbody>
</table>

Genetic predisposition may be important in the pathogenesis of esophageal squamous cell cancer. Case-controlled studies have identified familial aggregation, suggesting that the cancer may be heritable. Mitochondrial studies have proved historical population migrations from central-northern to southern-eastern China, where another high-incidence area is found, again suggesting that hereditary factors may play a part. Genetic polymorphism is important in individuals with chronic alcohol consumption. Approximately 36% of East Asians show a physiologic
response to drinking that includes facial flushing, nausea, and tachycardia. This facial flushing response is predominantly related to an inherited deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2). Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and the acetaldehyde is, in turn, metabolized by ALDH2 to acetate. Two main variants for ALDH2 exist, resulting from the replacement of glutamate with lysine at position 487. Only individuals homozygous for the glutamate allele have normal catalytic activity. Homozygotes with the lysine alleles have no detectable activity, whereas heterozygotes with Glu/Lys alleles have much reduced ALDH2 activity. The inability to fully metabolize acetaldehyde results in its accumulation in the body, leading to the facial flushing and unpleasant side effects. Lys/Lys homozygotes could not tolerate much alcohol because of the intensity of the side effects, and so paradoxically, they do not have increased risk because they simply do not consume a significant amount of alcohol. Individuals who are Glu/Lys heterozygotes may become habitual drinkers because they can become tolerant to the side effects of alcohol and yet have suboptimal catalytic activity, and thus the acetaldehyde accumulates. These are the individuals most susceptible to the carcinogenic effects of alcohol consumption, which are related to acetaldehyde causing DNA damage and other cancer-promoting effects.\textsuperscript{13} A simple questionnaire that elicits the history of a flushing response was shown to be useful in identifying at-risk individuals. They could be advised against drinking or to undergo screening endoscopy. The risk of developing cancer may be reduced or earlier diagnosis possible.\textsuperscript{14}

For squamous cell cancer, in addition to drinking and smoking, dietary and environmental factors are important, especially in Asian countries. Nitrosamines and their precursors (nitrate, nitrite, and secondary amines), such as pickled vegetables, are incriminated.\textsuperscript{15} Nutritional depletion of certain micronutrients, particularly vitamins A, C, and E, niacin, riboflavin, molybdenum, manganese, zinc, magnesium selenium, as well as inadequate consumption of fresh fruits, vegetables, and protein, predispose the esophageal epithelium to neoplastic transformation.\textsuperscript{16} Changes in specific dietary habits, such as replacing traditional methods of food preservation and storage with refrigeration, together with consumption of vitamin-rich food, may have produced a drop in incidence rates in certain areas of China, especially in urban cities such as Shanghai.\textsuperscript{17} Other dietary risk factors include consumption of hot beverages, opium smoking, chewing betel nuts,
and mate drinking in South American countries.

The human papillomaviruses and certain fungi belonging to the genera *Fusarium*, *Alternaria*, *Geotrichum*, *Aspergillus*, *Cladosporium*, and *Penicillium* are infective agents variably found to be associated with esophageal cancer.

Patients with other aerodigestive malignancies have a particularly high risk of developing squamous cell carcinoma (SCC) of the esophagus, presumably because of exposure to similar environmental carcinogens and “field cancerization.” Using esophageal cancer as the index tumor, multiple primary cancers were found in 9.5% of patients, of which 70% were in the aerodigestive tract. The overall incidence of synchronous or metachronous esophageal cancer in patients with primary head and neck cancer is estimated to be 3%.

Diseases that are known to predispose to esophageal cancer are few. The risk from achalasia is estimated to be 7- to 33-fold, but symptoms of achalasia are present for an average of 15 to 20 years before the emergence of cancer. Other diseases include lye corrosive strictures, Plummer-Vinson syndrome, tylosis, and celiac disease.

For adenocarcinoma, the reasons to account for the significant rising incidence can be attributed to the obesity epidemic, gastroesophageal reflux disease, and Barrett esophagus, which are less common in Asian populations, with the reported prevalence of Barrett esophagus ranging from 0.06% to 19.9% in Asia. Gastroesophageal reflux disease affects up to 44% of the general population in the United States, and approximately 5% to 8% will develop Barrett esophagus, with an estimated annual rate of neoplastic transformation of 0.1% to 0.3%. The degree of dysplasia is associated with the risk of malignant transformation, with an annual rate of 0.25% for patients without dysplasia and 6% for patients with high-grade dysplasia. Epidemiologic data suggest a protective role of *Helicobacter pylori* against reflux. The high prevalence of *H pylori* infection in Eastern populations may guard against reflux and Barrett esophagus and may account for the difference in cancer cell type. However, this association remains controversial.

**DIAGNOSIS**
Early Neoplastic Lesions

SQUAMOUS CELL DYSPLASIA

Diagnosing esophageal cancer at an early stage is crucial in improving the prognosis. The 5-year survival rate is approaching 90%, and a 25-year survival rate of 50% can be achieved when cancer is diagnosed at an early stage.\(^{29}\) In high-incidence countries such as China and Japan, national screening programs aim at early diagnosis.

The initial technique of screening in China was to use an inflatable balloon that was swallowed and retrieved to obtain abrasive cytology, whereas in Japan, a cytology sample was harvested using an encapsulated sponge.\(^{30,31}\) This type of screening cytology has been replaced by primary endoscopic examination in high-risk areas or in populations at increased risk. Traditionally, chromoendoscopy using Lugol’s iodine is a useful adjunct (Fig. 26-1). In addition, there is significant advancement of endoscopic technology to detect early neoplastic lesions. The development of narrow-band imaging allows optical chromoendoscopic examination. A high-resolution or magnifying endoscopy allows detail examination of mucosal capillary pattern and detection of early neoplastic neovascularization. A classification system of the intraepithelial papillary capillary loop (IPCL) has been introduced to grade the severity of these early neoplastic changes (Fig. 26-2).\(^{32}\)
FIGURE 26-1 A. Endoscopy using Lugol’s iodine stain. The unstained area is the abnormal region. B. Narrow-band imaging of the same region.

FIGURE 26-2 A. Classification of intraepithelial papillary capillary loop (IPCL) and recommended treatment strategies. B. Blue arrow, type I IPCL; red arrow, type V-1 IPCL. C. Blue arrow, type V-2 and V-3; red arrow, type
BARRETT ESOPHAGUS AND ADENOCARCINOMA

Screening and surveillance for early cancer due to Barrett esophagus are controversial. Gastroesophageal reflux is prevalent among the white populations; approximately 20% of adults have heartburn at least once per week, 5% of whom have Barrett esophagus; thus, a very substantial number of patients will require screening. However, the absolute risk of adenocarcinoma is low even in subgroups of patient with severe reflux symptoms. Moreover, 40% or more of patients with esophageal adenocarcinoma have no prior reflux symptoms and therefore would not be detected through screening programs targeted to those with such reflux symptoms. Current guidelines suggest that for patients with an established diagnosis of Barrett esophagus, surveillance is recommended. Systemic 4-quadrant, 2-cm biopsy protocol using jumbo biopsy forceps is recommended. Dysplasia is so far the only reliable indicator of risk for development of invasive cancer. The recommendations given by the American College of Gastroenterology with regard to endoscopy interval and treatment are listed in Table 26-2.
Endoscopy and systemic biopsies remain the gold standard for diagnosis of Barrett esophagus, dysplasia, and early cancer. Other modalities such as cytology (with or without fluorescence in situ hybridization [FISH]), autofluorescence imaging, narrow-band imaging, optical coherence tomography, and confocal laser endomicroscopy are investigational techniques aimed at enhancing diagnostic capabilities.\(^{35}\) It has been reported that acetic acid chromoendoscopy can increase diagnostic yield of Barrett esophagus by 6 times and the number of biopsies required to detect 1 neoplasia was 15 times fewer compared conventional protocol based biopsy approach.\(^{36}\)

### Advanced Cancer

Evaluation of symptoms, physical signs, and demographic factors helps in the diagnosis of advanced cancer. Patients may present with different symptoms depending on the extent of disease. Elderly patients complaining of dysphagia must be assumed to have esophageal cancer until proven otherwise. Patients with chronic reflux symptoms who develop dysphagia must have tumor in the differential diagnosis in addition to reflux stricture.

In advanced disease, the most common presenting symptom is dysphagia (80%-95%) that is progressive in severity. Many patients delay seeking medical advice until severe dysphagia and weight loss have occurred.
Regurgitation is common, especially when the patient lies supine at night. Fluid regurgitation can lead to coughing, aspiration, and chest infection. Food boluses passing the tumor site may cause retrosternal pain (odynophagia). Hoarseness is the result of tumor invasion of the recurrent laryngeal nerve either by the primary tumor or nodal metastases.

The demographics of patients with SCC are different from those of patients with adenocarcinoma (Table 26-3). Patients with SCC are usually blue-collar workers with recent significant weight loss. Chronic smoking and alcohol consumption are common and lead to a higher prevalence of chronic lung disease and liver cirrhosis. A proximally located tumor more easily predisposes to aspiration pneumonia from regurgitated fluid and, in advanced cancer, tracheoesophageal fistula. Supraclavicular regions should be examined for the presence of nodal spread. Patients with adenocarcinoma usually come from a higher socioeconomic class. Adenocarcinomas are associated with obesity-related diseases such as gastroesophageal reflux disease and ischemic heart disease.

**TABLE 26-3: DEMOGRAPHICS OF SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA OF THE ESOPHAGUS**
STAGING

Accurate staging allows stage-directed therapies and quality control for clinical trials. To achieve this, an evidence-based staging system and comprehensive modalities of investigation are crucial.

Staging System

The most commonly used staging system worldwide is the American Joint Committee on Cancer (AJCC) staging and the International Union Against Cancer (UICC) TNM (tumor-node-metastasis) system.

The definitions of TNM, tumor grade, level of tumors, and nodal stations are shown in Tables 26-4 to 26-11 and Figures 26-3 and 26-4. The T stage advances as tumor invades from mucosa deep to muscle, adventitia, and beyond the esophagus. Regional nodes encompass areas from the neck and through the mediastinum to the upper abdomen, including the celiac nodes.

<table>
<thead>
<tr>
<th></th>
<th>SCC</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor location</td>
<td>Mid and lower esophagus</td>
<td>Lower esophagus/cardia</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Pulmonary disease, Liver cirrhosis</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Premalignant lesions</td>
<td>Dysplasia</td>
<td>Barrett esophagus and dysplasia</td>
</tr>
<tr>
<td>Screening/surveillance</td>
<td>Balloon cytology, Endoscopic with Lugol’s iodine</td>
<td>Endoscopy surveillance</td>
</tr>
<tr>
<td>Surgical approaches</td>
<td>Predominantly transthoracic, 2-/3-field lymphadenectomy, Thoracoscopic ± laparoscopic</td>
<td>Transthoracic/transhiatral, 2-field or minimal lymphadenectomy, Thoracoscopic ± laparoscopic or laparoscopic only</td>
</tr>
</tbody>
</table>

Abbreviation: SCC, squamous cell carcinoma.
The segregation of N1 to N3 is by the number of involved lymph nodes. Location is defined by the position of the epicenter of the tumor in the esophagus and classified as X: location unknown; Upper: cervical esophagus to lower border of azygos vein; Middle: lower border of azygos vein to lower border of inferior pulmonary vein; and Lower: lower border of inferior pulmonary vein to stomach, including gastroesophageal junction. Squamous cell cancers are stage-grouped differently to adenocarcinoma. Stage-groups of both tumor types are further sub-classified as clinical (cTNM); post-neoadjuvant (ypTNM) and pathological (pTNM) stage according to the latest 8th edition of AJCC staging system.

**TABLE 26-4: DEFINITIONS OF TNM FOR ESOPHAGEAL CANCER**
### T: Primary tumor

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades the lamina propria, muscularis mucosae, or submucosa</td>
</tr>
<tr>
<td></td>
<td>T1a: Tumor invades the lamina propria or muscularis mucosae</td>
</tr>
<tr>
<td></td>
<td>T1b: Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades the muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades adventitia</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades the adjacent structures</td>
</tr>
<tr>
<td></td>
<td>T4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum</td>
</tr>
<tr>
<td></td>
<td>T4b: Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway</td>
</tr>
</tbody>
</table>

### N: Regional lymph nodes*

<table>
<thead>
<tr>
<th>Code</th>
<th>Definition</th>
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<tr>
<td>Nx</td>
<td>Regional nodal status cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in one or two regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in three to six regional lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in seven or more regional lymph nodes</td>
</tr>
</tbody>
</table>

### M: Distant metastases

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<th>Definition</th>
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</thead>
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<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

TNM, tumor-node-metastasis.  
*Regional nodes extend from the neck to the celiac nodes.  
**TABLE 26-6: CLINICAL STAGE GROUPINGS FOR SQUAMOUS CELL CARCINOMA (cTNM)**

**Squamous cell carcinoma G category**
GX  Differentiation cannot be assessed
G1  Well differentiated
G2  Moderate differentiated
G3<sup>a</sup>  Poorly differentiated, undifferentiated

**Adenocarcinoma G category**
GX  Differentiation cannot be assessed
G1  Well differentiated, with >95% of the tumor composed of well-formed glands
G2  Moderately differentiated, with 50-95% of the tumor showing gland formation
G3<sup>b</sup>  Poorly differentiated, with tumors composed of nest and sheets of cells with <50% of the tumor demonstrating glandular formation

<sup>a</sup>If further testing of “undifferentiated” cancers reveals a squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.

<sup>b</sup>If further testing of “undifferentiated” cancers reveals a glandular component, categorize as adenocarcinoma G3.

**TABLE 26-7: POST-NEOADJUVANT THERAPY STAGE GROUPINGS FOR SQUAMOUS CELL CARCINOMA (ypTNM)**

<table>
<thead>
<tr>
<th>ypTNM stage</th>
<th>ypT</th>
<th>ypN</th>
<th>ypM</th>
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<tbody>
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<td>I</td>
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</tr>
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<td>N0</td>
<td>M0</td>
</tr>
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<td>T0-2</td>
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<td>M0</td>
</tr>
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<td>N1</td>
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</tr>
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<td>M0</td>
</tr>
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<td>N0-2</td>
<td>M0</td>
</tr>
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</tr>
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<td>Any N</td>
<td>M1</td>
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**TABLE 26-8: PATHOLOGICAL STAGE GROUPINGS FOR SQUAMOUS CELL**

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<th>cTNM Stage</th>
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<th>cM</th>
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</thead>
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<td>M0</td>
</tr>
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<td>N0-1</td>
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<td>N0-1</td>
<td>M0</td>
</tr>
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</tr>
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### TABLE 26-10: POST-NEOADJUVANT THERAPY STAGE GROUPINGS FOR ADENOCARCINOMA (ypTNM)

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<th>cN</th>
<th>cM</th>
</tr>
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<tbody>
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</tr>
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</thead>
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FIGURE 26-3  Description of the different levels of esophageal tumor. Ae, abdominal esophagus; B, tracheal bifurcation; Ce, cervical esophagus; D, diaphragm; EGJ, esophagogastric junction; H, hiatus; Lt, lower third; Mt, middle third; O, esophagus; S, sternal notch; Te, thoracic esophagus; Ut, upper third.
Controversy exists regarding whether adenocarcinoma of the gastroesophageal junction (GEJ) should be staged as esophageal or gastric cancer. Adenocarcinoma of the cardia was staged as esophageal cancer according to the seventh edition of the AJCC staging system. However, assigning tumors at this location as esophageal or gastric is somewhat arbitrary. Since the launch of the seventh edition of the AJCC staging system in 2010, accumulating evidence, especially from the East (eg, Japan and Korea), has suggested that type III tumors should be staged as gastric cancer instead of esophageal cancer. The definition of esophagogastric junction is thus revised in the 8th edition of AJCC system such that cancer involving it with epicenters no more than 2 cm into the gastric cardia are
staged as adenocarcinoma of the esophagus and those with more than 2cm involvement of the gastric cardia are staged as stomach cancer, even if the edges of the tumors invades the esophagogastric junction.\textsuperscript{39}

In daily practice, an anatomic classification system for adenocarcinoma of the GEJ that is widely adopted is the Siewert classification. This assigns tumors 5 cm proximal and distal to the GEJ into types I to III (esophageal, cardiac, and subcardiac; \textbf{Fig. 26-5}). The three types of cancers differ in regard to patient demographics, possible etiology, histopathologic features, treatment approach, and prognosis. Although widely recognized with much data to support the classification, there are certain drawbacks to this system. First, assigning tumors to type I to III may lack accuracy preoperatively, especially when advanced tumors may have obliterated the landmarks endoscopically; the system classifies tumors by the epicenter of the tumor. Second, treatment, especially surgical approaches, would more depend on the proximal and distal extent of the tumors rather than the epicenter; for instance, a small tumor of 2 cm centered on the GEJ is approached quite differently from a 10-cm tumor that also centers on the GEJ. This has to be kept in mind before using this system.
FIGURE 26-5  

A. Classification of adenocarcinomas around the gastroesophageal junction (GEJ) according to Siewert. Type I, esophageal; type II, cardiac type III, subcardiac.  

B. A type I adenocarcinoma arising from Barrett esophagus. The large arrow points at the gastroesophageal junction (GEJ), whereas the small arrow points at the squamocolumnar junction.  

C. A type II cardia cancer removed as a total gastrectomy specimen and its corresponding barium contrast study. There is no evidence of Barrett esophagus.

METHODS OF STAGING

The modalities to achieve precise staging include barium contrast studies, bronchoscopy, upper endoscopy, computed tomography (CT) scan, percutaneous ultrasound of cervical lymph nodes with or without fine-needle aspiration (FNA) cytology, endoscopic ultrasound (EUS) with or without FNA, 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scan, and laparoscopy and/or thoracoscopy.

Barium Contrast Studies

The availability of other new staging modalities makes barium contrast studies much less essential. Features indicative of presence of malignancy include mucosal irregularity, shouldering, stenotic lumen, and dilatation of proximal esophagus (Fig. 26-6). Other signs that are suggestive of advanced-stage disease include tortuosity, angulation, axis deviation from the midline, sinus formation, and fistulation to the tracheobronchial tree.
FIGURE 26-6  Barium contrast swallow showing a stenotic tumor. Mucosal irregularities and proximal dilation with retention of contrast material are evident. A sinus often indicates infiltrative disease (arrow).

**Bronchoscopy**

Bronchoscopy is performed to assess tumor invasion of the tracheobronchial tree, especially for proximally located tumors. Signs indicative of tumor involvement include widening of carina, extrinsic compression particularly from posterior tracheal wall, direct tumor infiltration, and fistulization.
Histopathologic confirmation of tumor invasion of the tracheobronchial tree precludes upfront surgical resection.

**Computed Tomography Scan**

The main value of CT scan in the staging of esophageal cancer is its ability to detect distant metastasis, such as that in liver, lung, bone, and kidneys. The sensitivity for liver metastases larger than 2 cm is approximately 70% to 80%, but sensitivity is reduced to 50% if the lesion is <1 cm.\(^\text{39}\) Lung metastasis is seldom a solitary lesion, and if it presents as a solitary mass, investigation should be directed to primary lung cancer or benign nodules.

In evaluation of the primary esophageal tumor, the precision of CT scan is inferior to EUS. In the diagnosis of T4 disease by CT scan, obliteration of the fat plane between the esophagus and the aorta, trachea and bronchi, and pericardium is suggestive of invasion, but the paucity of fat in cachectic patients makes this criterion unreliable. When the area of contact between the esophagus and the aorta extended for more than 90 degrees of the circumference, an 80% accuracy of infiltration was reported,\(^\text{40}\) but this is by no means absolute.

The sensitivity of detecting mediastinal and abdominal nodal involvement is suboptimal with CT scans because only size alone can be used as diagnostic criterion. However, normal-sized lymph nodes may contain metastatic deposits, and enlargement of lymph nodes may be due to reactive and inflammatory hyperplasia. Studies using high-resolution helical CT scanning have demonstrated sensitivities of 11% to 77% and specificities of 71% to 95% for detection of regional nodal disease.\(^\text{41}\) CT scanning is now commonly performed together with PET scanning; a composite picture is created in the same setting to correlate more accurate anatomy with metabolic uptake (Fig. 26-7).
FIGURE 26-7 Combined positron emission tomography (PET) and computed tomography image. In addition to size of lymph nodes, the standard uptake value (SUV) often will help to determine if the lymph node is involved by cancer. A right pulmonary hilar node identified with its corresponding PET image. SUV was 3.1.

Endoscopic Ultrasound and Percutaneous Ultrasound

EUS is the only imaging modality able to distinguish the various layers of the esophageal wall, usually seen as 5 alternating hyper- and hypoechoic layers (Fig. 26-8). The accuracy of EUS for tumor and nodal staging averages 85% and 75%, respectively, compared to 58% and 54% for CT scanning. In about one-third of patients, a conventional EUS probe cannot pass through the esophageal lumen due to tumor stricture. Miniaturized ultrasound catheter probes can be used to pass through the working channel of a conventional endoscope, which can achieve comparable accuracy to conventional EUS. A study found that predilation is safe in this situation, but the success rate of complete examination depends on the size of dilation (36% for 11-12.8 mm and 87% for 14-16 mm).
FIGURE 26-8  Endoscopic ultrasound (EUS) picture of an early tumor confined to the mucosa. Five layers of the esophagus can be seen; the 2 dark layers are the muscularis mucosae (inner layer) and muscularis propria (outer layer). In this tumor, the hyperechoic layer of the submucosa has not been reached. The tumor is at 6 o’clock. This lesion was removed with endoscopic submucosal dissection (ESD) technique.

Echo features of lymph nodes that suggest malignant involvement include echo-poor (hypoechoic) structure, sharply demarcated borders, rounded contour, and size greater than 10 mm, in increasing order of importance. A collective review showed that the overall accuracy of staging nodal disease was 77%. The accuracy of EUS may differ for different lymph node locations and is related to the depth of penetration of EUS (about 3 cm). It is best for detecting paraesophageal nodes, and sensitivity varies inversely with the axial distance of the nodes from the esophageal axis. The ability to perform EUS-guided FNA cytology of suspicious nodes (such as celiac
nodes) is another factor that makes EUS superior to CT scanning. Percutaneous ultrasound is particularly useful for obtaining FNA biopsies of cervical lymph nodes. In one large study of 519 patients, cervical lymph node metastasis was detected in 30.8% of patients (160 of 519 patients). The sensitivity, specificity, and accuracy of US diagnosis in patients who underwent subsequent cervical lymphadenectomy were 74.5%, 94.1%, and 87.6%, respectively. In those who did not undergo neck dissection, the chance of cervical nodal recurrence was low, at less than 5%.\textsuperscript{43}

Information gained by combining preoperative cervical ultrasound and EUS can be highly prognostic. In one study, when the number of metastatic nodes was stratified into subgroups of 0, 1 to 3, 4 to 7, and 8 or more nodes, the number of involved lymph nodes was prognostically similar to the eventual subdivisions as determined by histologic diagnosis.\textsuperscript{44} However, both percutaneous ultrasound and EUS are highly operator-dependent, and meticulous application is required to produce these results.

**FDG-PET Scans**

PET is gaining popularity in esophageal cancer staging and is commonly used in conjunction with CT scans for better anatomic definition. For detecting the primary tumor, the sensitivity of PET ranges from 78% to 95%, with most false-negative tests occurring in patients with T1 or small T2 tumors.\textsuperscript{41,45} Adenocarcinomas of the GEJ and proximal stomach sometimes show limited or absent FDG accumulation regardless of tumor volume (FDG nonavidity). Some investigators observed this phenomenon in as many as 20% of these patients, and it seems to be related to the diffusely growing subtype and poorly differentiated tumors.\textsuperscript{46}

PET does not provide definition of the esophageal wall and thus has no value in determining T stage. For locoregional nodal metastases, its spatial resolution is also insufficient to separate the primary tumor from juxtatumoral lymph nodes because of interference from the primary tumor, and thus, most studies demonstrated poor sensitivity. This is especially true for nodes in the middle and lower mediastinum, where most primary tumors are found. In one study, the sensitivities of PET for detecting cervical, upper thoracic, and abdominal nodes were 78%, 82%, and 60%, respectively, but were only 38% and 0%, respectively, for the mid and lower mediastinum.\textsuperscript{41} Specificity of
PET in detecting regional nodes is usually much better, reaching 95% to 100% in some studies.\textsuperscript{45,47} The low rate of false-positive findings is important in preoperative staging.

A meta-analysis of 12 publications on PET scanning in esophageal cancer showed that the pooled sensitivity and specificity for the detection of locoregional metastases were 0.51 (95% confidence interval [CI], 0.34-0.69) and 0.84 (95% CI, 0.76-0.91), respectively. For distant metastases, the corresponding figures were 0.67 and 0.97. When 2 studies (out of 11) that had particularly low sensitivities for detection of distant metastases were excluded (probably because they included more early tumors), the pooled sensitivity improved to 0.72 and specificity to 0.95.\textsuperscript{48} This study highlights that the accuracy of PET in locoregional nodes is only moderate.

**Thoracoscropy and Laparoscopy**

Thoracoscropy and laparoscopy have their advocates. Thoracoscopic staging usually involves a right-sided approach, with opening of the mediastinal pleura from below the subclavian vessels to the inferior pulmonary vein with lymph node sampling. Laparoscopic staging can include celiac lymph node biopsy and the use of laparoscopic ultrasound for detecting liver metastases. One multi-institutional study (CALGB 9380) reported results in 113 patients, and the strategy was feasible in 73% of patients. Thoracoscopy and laparoscopy identified nodes or metastatic disease missed by CT scan in 50% of patients, by magnetic resonance imaging (MRI) in 40%, and by EUS in 30%. Although no deaths or major complications occurred, this approach did involve general anesthesia, one-lung anesthesia, a median operating duration of 210 minutes, and a hospital stay of 3 days.\textsuperscript{49} Laparoscopy could be used in diagnosing metastases (especially peritoneal spread) or identifying unsuspected cirrhosis, which may contraindicate resection, and it could be performed as a preliminary procedure during the time of esophagogastrectomy. Its main contribution would be in lower esophageal and cardiac adenocarcinoma, whereas its value is expected to be minimal for more proximally located tumors.\textsuperscript{50} Given their invasiveness, thoracoscopy and laparoscopy should be reserved for patients in whom positive confirmation of metastatic disease is not otherwise obtainable and is essential in deciding on treatment.
TREATMENT

Stage-Directed Therapy

Treatment options for esophageal cancer were limited in the past. Surgical resection, radiotherapy, and plastic stenting for palliation were the only 3 choices. With the advancement of technology, there has been a proliferation of therapeutic options. Staging has becoming increasing more important in stratifying patients for different treatment methods, either alone or in combination with others.

Early Squamous Cell Cancers

Early tumors include T1a-EP, LMP, MM and T1b-SM1, SM2, and SM3 lesions as defined in Table 26-12. The risk of nodal metastases is the most important factor to consider in choosing the therapeutic option. The reported rates of nodal involvement in T1a-EP, T1a-LMP, and T1a MM tumors are 0%, 3.3%, and 12.2%, respectively. For T1b-SM1, SM2, and SM3 lesions, the respective rates of lymph node involvement are 26.5%, 35.8%, and 45.9%, respectively. Five-year survival rates are 80% to 100% for mucosal cancers and 50% to 65% for submucosal cancers.

TABLE 26-12: CLASSIFICATION OF T1 TUMORS ACCORDING TO THE JAPAN ESOPHAGEAL SOCIETY
Tumors with minimal risk of nodal metastases, such as T1a-EP and LMP, are amenable to endoscopic mucosal resection (EMR). Circumferential mucosal resection may result in cicatricial stenosis. Therefore, EMR is indicated for lesions not exceeding two-thirds of the circumference of the esophagus. EMR can also be a feasible treatment for tumors of moderate risk of nodal metastases such as T1a-MM or T1b-SM1 (200 μm deep from the muscularis mucosa) but without evidence of nodal spread in pretreatment staging investigation. SM2 and SM3 lesions are associated with significant risk of nodal metastases and should be treated with the same approach as in advanced cancers. The distinction of SM2/SM3 lesions from more superficial ones, however, is difficult, even with high-frequency EUS. In practice, therefore, these tumors are often resected endoscopically based on endoscopic appearance and the experience of the endoscopist. The resected specimens are then examined histologically to assess depth of infiltration and hence curability. A decision is then made regarding whether additional
treatment would be needed. The Japan Esophageal Society has published guidelines on the treatment for early cancers, especially regarding the indications for endoscopic resection.\textsuperscript{52} Clinical trials are also being carried out to enhance local control and cure rate of endoscopic resection, such as the addition of radiotherapy in preventing local recurrence.\textsuperscript{53}

Endoscopic resection techniques include EMR and endoscopic submucosal dissection (ESD). EMR is performed by injection of saline into the submucosal plane to raise the mucosal lesion. The lesion is then sucked into a cap fitted onto the tip of endoscope, looped by a snare wire, and cut by blend-current electrocautery. The limitation of this technique is that the size of the lesion should be less than the size of the cap, and the generally recommended size of the lesion should be less than 2 cm. For larger lesions, if resected by EMR, complete resection can only be achieved with piecemeal resection, which is associated with increased recurrence rate when compared to ESD.

ESD is more complex. There are several steps in ESD, as follows: (1) marking: the border of the lesion is marked by electrocautery; (2) submucosal injection: injection of solution into the submucosal tissue plane; (3) precut: cutting the mucosal edges along the line of marking; (4) submucosal dissection: dissecting the lesion from the submucosal bed; and lastly (5) hemostasis. There are various types of solutions used for submucosal injection; examples include glycerol, hyaluronic acid, hypertonic saline, and mannitol. The common feature of these solutions is that they can be retained in the tissue plane longer to delay dispersion. Methylene blue or indigo carmine can be added for better visualization and adrenaline to improve hemostasis. Different through-the-scope instruments are available for the cutting and dissection; the choice is mainly based on endoscopist preference. Comparing ESD with EMR, ESD has less chance of positive margins, more en-bloc resection, and lower recurrence rate, but it has slightly higher bleeding and perforation rates. The technique for ESD is more demanding, and the learning curve is longer.

For ablative therapy, radiofrequency ablation (RFA) has been applied for squamous esophageal dysplastic lesions.\textsuperscript{54} The advantage is that it is technically easy to operate, but the drawback is that no surgical specimen for detailed histopathologic examination is available.
Early Adenocarcinoma and High-Grade Barrett Dysplasia

Barrett high-grade dysplasia, synonymous with intraepithelial cancer, is the last preinvasive stage in the metaplasia-dysplasia-cancer sequence. Treatment options include intensive surveillance, mucosal ablation, and esophagectomy.

INTENSIVE SURVEILLANCE

Proponents of endoscopic surveillance claim that such a strategy can diagnose invasive cancer at an early stage and treatment can be delayed until then without compromising prognosis. The assumed high morbidity and mortality rates of esophagectomy are also a deterrent to immediate surgical resection. Opponents of surveillance observe that the incidence of early adenocarcinoma or high-grade dysplasia is estimated at 1.1% to 6% annually, but some estimates are as high as 13.4% per year.\textsuperscript{25,26,55} High-grade dysplasia is currently the only reliable marker of preinvasive cancer, but interobserver concordance is suboptimal in distinguishing invasive and noninvasive lesions. When esophagectomy is carried out in patients who have high-grade dysplasia, invasive cancer is identified in the surgical specimen in up to 42% of patients, even when patients have been recruited in surveillance programs. More recent evidence, however, suggests that this figure is an overestimate; a meta-analysis of histologic findings after esophagectomy for high-grade dysplasia revealed invasive adenocarcinoma (at least submucosal cancer) in 12.7% of patients, and most of these patients had visible lesions such as nodularity at endoscopy, a known risk for invasive cancer. In the absence of visible lesions, this figure is as low as 6.7%.\textsuperscript{56} Most would regard the finding of high-grade dysplasia as a threshold for intervention. In patients who have visible lesions, such as raised nodules, and not just a flat Barrett mucosa, endoscopic resection is recommended to ensure no invasive cancer is present, followed by ablative therapy of the remaining flat columnar mucosa. Given the high incidence of progression from high-grade dysplasia to early adenocarcinoma, current guidelines recommend intervention, preferable with endoscopic therapy (Tables 26-2 and 26-13).\textsuperscript{34}
TABLE 26-13: PRACTICE GUIDELINES FOR BARRETT ESOPHAGUS FROM PROFESSIONAL BODIES

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<th>HGD</th>
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Abbreviations: AGA, American Gastroenterological Association; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NA, not applicable; NDBE, nondysplastic Barrett esophagus; NICE, National Institute for Health and Clinical Excellence; RFA, radiofrequency ablation. SAGES: South African Gastroenterology Society. *SAGES, Society of American Gastrointestinal and Endoscopic Surgeons.

ENDOSCOPIC THERAPIES

The rationale of endoscopic mucosal treatments is that the incidence of nodal metastases is low in high-grade dysplasia or T1a (intramucosal) cancers, and therefore, treating the mucosal disease alone will result in cure. In T1a lesions, the rate of nodal metastases is low, reported as 0% to 6%. Once the submucosa is invaded (T1b lesions), this figure rises to around 20%.57

Several professional bodies have launched practice guidelines for endoscopic treatment for Barrett esophagus (Tables 26-2 and 26-9). The
options of endoscopic approaches for high-grade dysplastic Barrett esophagus and early adenocarcinoma include EMR, photodynamic therapy (PDT), and RFA.

EMR can be used to resect localized visible lesions in Barrett esophagus. A study of EMR reported by Ell and colleagues\textsuperscript{58} included 100 patients, of whom complete local remission was achieved in 99%. Eleven percent of patients developed recurrence (6% locally and 5% at different locations), but successful repeated treatments were possible in all. The 5-year survival rate was 98%.\textsuperscript{58} In this study, all patients had mucosal lesions of up to 20 mm, no lymphovascular invasion, and histologic grades of G1 and G2 arising in Barrett metaplasia.

In addition to resecting the localized lesions, circumferential EMR is possible to deal with the whole length of the Barrett mucosa. In one series, the complete resection rate was 76%. With a median follow-up of 32 months, however, recurrent or metachronous early cancer was found in 12% of patients.\textsuperscript{59}

In addition to resectional therapy, ablative methods are available. A randomized trial demonstrated that PDT could reduce the cancer risk in Barrett esophagus. In this study, 208 patients with high-grade dysplasia were randomized to ablation using PDT with porfimer sodium plus a proton pump inhibitor (PPI) versus PPI only. High-grade dysplasia was eliminated in 77% of patients in the PDT group, although in 39% of patients in the PPI group, high-grade dysplasia was also lost on subsequent biopsies. Barrett epithelium elimination was achieved in 52% of patients in the PDT compared to 7% in the PPI group. Adenocarcinoma developed in 15% of the patients in the PDT group compared with 29% in the PPI group, with a longer time to progression to cancer favoring PDT.\textsuperscript{60} The problems with PDT treatment include the need for repeated sessions, photosensitivity, stricture formation (6% in the series just described), and the phenomenon of buried glands or pseudo-regression, making continual surveillance necessary. This incidence can be as high as 51%. Because PDT does not treat nodal disease and there is no specimen for histologic examination, accurate pretherapy diagnosis of noninvasiveness is necessary.

RFA has been shown to be effective in treating both nondysplastic and dysplastic Barrett esophagus. RFA energy is delivered by bipolar electrode and the energy causes frictional heating of cellular water molecules. The
system comes with circumferential (HALO360) and focal ablative probes (HALO90). Technically, the procedure is performed under sedation. For HALO360, a sizing balloon is first introduced into the esophagus and an appropriate size of probe is chosen and inserted into the esophagus. For HALO90, the probe is mounted at the tip of an endoscope. The ablative surface is a 20-mm-long × 13-mm-wide articulated platform with an electrode array identical to the circumferential device. It is best used for ablating residual Barrett mucosa after first treatment. There are other new devices available including a similar focal HALO90 size probe that is inserted through the biopsy channel of the scope.

The Ablation Intestinal Metaplasia-II (AIM-II) trial examined the use of the HALO system in ablating nondysplastic Barrett esophagus of up to 6 cm in length. HALO360 treatment was performed at baseline and repeated at 4 months if there was residual intestinal metaplasia. Focal ablation with HALO90 was carried out after 12 months if needed. Complete remission of metaplasia was achieved in 48 (70%) of 69 patients at 12 months and in 60 (98%) of 61 patients at 30 months. No stricture or buried glands were found.61

Another trial examined the use of the HALO system in ablating dysplastic Barrett esophagus; 127 patients were randomly assigned in a 2:1 ratio to RFA or to a sham procedure. Randomization was stratified according to the grade of dysplasia and the length of Barrett esophagus. Primary outcomes at 12 months included eradication rates of dysplasia and intestinal metaplasia. In the intent-to-treat analyses, among patients with low-grade dysplasia, complete eradication of dysplasia occurred in 90.5% of patients in the ablation group compared to 22.7% in the control group. Among patients with high-grade dysplasia, the respective figures were 81% and 19%. Overall, 77.4% of patients in the ablation group had complete eradication of intestinal metaplasia, compared with 2.3% of patients in the control group. Patients in the ablation group had less disease progression (3.6% vs 16.3%) and fewer cancers (1.2% vs 9.3%). Stricture only developed in 6% of ablated patients.62

A study recruited 1634 patients who achieved complete eradication for the investigation of recurrence. With an average follow-up of 2.4 years, 20% of patients had recurrence and the recurred length of Barrett mucosa was 0.6 cm, which was significantly shorter than the pretreatment length. The likelihood for recurrence was associated with increasing age, longer Barrett mucosal length, and nonwhite race.63
ESOPHAGECTOMY

Surgical resection is the only method to ensure complete eradication of the dysplastic mucosa and the frequently undetected invasive cancer. Surgical resection was considered a standard treatment because of the high frequency of invasive cancers found in surgical specimens when resection was performed for high-grade dysplasia (up to 42%), although more recent evidence suggests that this figure is much lower, at 13%.64 The supposedly high morbidity and mortality rates of esophagectomy are also deterrents against surgical resection. However, in specialized centers, the mortality rate from esophagectomy, especially in this group of patients, is minimal. Minimally invasive surgical methods, including thoracoscopy, laparoscopy, or esophageal stripping, further reduce the trauma of surgical access. Excellent long-term survival with good quality of life is reported.65

Vagal-sparing esophagectomy leaves the vagi intact and is another approach aimed at preserving quality of life; it has been shown to result in much fewer postvagotomy symptoms.66 In the Merendino procedure, limited surgical resection of the distal esophagus and GEJ, together with lymphadenectomy of the lower mediastinum and upper abdominal compartment, has also been advocated. An isoperistaltic jejunal interposition graft is used to restore intestinal continuity. This method combines the adequacy of nodal dissection and improved quality of life, as the jejunal loop prevents gastroesophageal reflux.67

In summary, in patients with high-grade dysplasia or early intramucosal cancer, treatment is indicated, preferably with endoscopic modalities. When the histopathologic findings of the specimen indicate more advanced than T1a, a multidisciplinary approach of management, as for advanced-stage disease, should be considered. Recent data showed that the risk of low-grade dysplasia progressing to early adenocarcinoma is low. It is controversial regarding whether surveillance or mucosal ablative therapy should be offered. The risk of progression in patients without dysplasia is even lower, and according to clinical practice guidelines, a surveillance interval of 3 to 5 years is appropriate.

Advanced Esophageal Cancer

Surgical resection remains the mainstay treatment for localized esophageal
cancer. Surgery in combination with multimodality treatment is also standard of care. Palliative methods have also improved when cure is not possible.

**SURGERY FOR ADVANCED ESOPHAGEAL CANCER**

Excellent surgical outcome after esophagectomy is now achievable in dedicated high-volume centers; centralization of services also improves outcome.\(^{68,69}\)

Important aspects to enhance better outcome after esophagectomy are (1) selecting appropriate patients for resection, (2) choice of surgical techniques and their execution, and (3) perioperative care.

**Patient Selection for Esophagectomy.** How stringently one selects patients for esophagectomy will influence the resection rate. Selection depends on many factors, including (1) the referral pattern of individual centers, (2) the prevailing treatment philosophy, (3) the availability of alternative therapies, and (4) the possible mortality that the surgeon and patient are prepared to accept. Reported resection rates range from 21% to 70% or 80%.\(^{70,71}\) This wide variation suggests probable prereferral bias or a high prevalence of early cancers in those with high resection rates.

In studies that report on improvement of surgical results over time, more stringent patient selection often comes into play, either by excluding high-risk patients or by treating advanced disease by nonoperative means. Resection with a clear aim for palliation is becoming uncommon, and most would only operate on patients for potential cure.

The evaluation of the fitness of a patient to undergo esophagectomy is an imperfect science. Many poor-risk indicators have been identified, such as Karnofsky score of less than 80,\(^{72}\) poor nutritional status as defined as more than 10% weight loss,\(^{73}\) preexisting cirrhosis, and cardiopulmonary disease.\(^{72}\) Other factors reported to be predictive of increased morbidity and mortality included advanced age, proximally located tumor, high alcohol intake, and heavy smoking.\(^{72,74}\) Certainly, evaluating risk is important in patient selection and in preoperative counseling. In practice, however, although certain conditions can be medically optimized, there is a limit in how much the preexisting physiologic reserve of patients can be improved. Perhaps the only exception is that when significant coronary ischemia is discovered, coronary revascularization with angioplasty and stenting could be performed.
Antiplatelet agents may delay surgery. It is prudent then to treat the patient first with neoadjuvant therapy while waiting for surgery. Cessation of smoking and alcohol intake is beneficial, and chest physiotherapy and incentive spirometry should be instituted.

**Choice of Surgical Approaches.** There are many important variables in esophagectomy, such as surgical access, the extent of resection and lymphadenectomy, the type and method of preparation of the esophageal substitute, the route of reconstruction, and the technique of esophageal anastomosis. Many of these variables are interrelated and could affect immediate morbidity and mortality rates, long-term quality of life, and survival. Tumor location and stage, patient risk profile, and surgeon preference and experience are important variables in deciding the surgical procedure. The surgeon should be versatile and well versed with the many different techniques to adapt to different clinical situations.

**Cervical Esophageal Cancer.** The incidence of cervical esophageal cancer accounts for 2% to 10% of all esophageal carcinomas. Pharyngolaryngoesophagectomy (PLE), with or without adjuvant radiotherapy, has been the gold standard of treatment since first reported by Ong and Lee in 1960. The procedure involves cervical and abdominal incisions and a thoracotomy. Tumors located at the hypopharyngeal and cervical esophageal regions were resected together with the whole length of the esophagus, and the gastric tube was pulled up to the neck via the posterior mediastinum for pharyngogastric anastomosis. A permanent end tracheostomy was created. Modern technique replaces the thoracotomy part with a transhiatal or minimally invasive approach. The outcomes of PLE have significantly improved over the past few decades. In the authors’ institute, the hospital mortality rate was brought down from 31% to 9%. It is still a complex procedure with relatively high morbidity and mortality rates compared with esophagectomy for intrathoracic esophageal cancer.

For tumors confined to the cervical esophagus, other alternative reconstructive methods are available, including free jejunal interposition graft (FJ), deltopectoral flap (DP), pectoralis major myocutaneous flap (PMF), free anterolateral thigh flap (ALT), and free posterior tibial flap (PTF) reconstruction. At the authors’ institute, in a series of 202 patients who had circumferential pharyngeal defects, the leakage rates using PMF, ALT, and
FJ for reconstruction were 23.9%, 12.5%, and 4.6%, respectively. The late anastomotic stricture rates for PMF, ALT, and FJ were 27.2%, 12.5%, and 2.3%, respectively, and overall graft failure occurred in 2% of patients. With manubrial resection, the distal extent of the FJ interposition is further lengthened, reaching the level above the aortic arch. FJ has become our preferred reconstructive method for circumferential pharyngeal defect since mediastinal dissection and its associated morbidities are avoided. FJ interposition can also be used when the gastric conduit is not long enough to reach the pharyngeal level, serving as a link between the gastric conduit and the pharyngeal defect above (Fig. 26-9).

FIGURE 26-9 Free jejunal graft to bridge the gap between gastric conduit and pharynx.

With the possibility of laryngeal preservation when treated by chemoradiation therapy, however, surgery is often not the preferred first choice of treatment. Therefore, the current role of surgery for cervical esophageal cancer is mainly for salvage after incomplete response or recurrent disease after chemoradiotherapy. Expectedly, surgery is made more complicated in heavily irradiated tissue when these situations arise.
**Intrathoracic Esophageal Cancer and Cardia Cancer.** Surgical resection for tumors located in the intrathoracic segment of the esophagus entails resection of the diseased segment with adequate margin and thorough lymphadenectomy. Optimal surgical approach depends on the location of the tumor.

For upper third tumors, a 3-phase esophagectomy (MaKeown approach) is an appropriate choice with the purpose of gaining adequate proximal margin. The intrathoracic segment of esophagus is first mobilized by right thoracotomy, followed by laparotomy for preparation of the gastric conduit, and lastly pull-up to the neck for esophagogastric anastomosis.

In Asia, most esophageal tumors are located in the middle third and are predominantly SCCs, whereas in the West, adenocarcinomas located at the lower third and around the GEJ have become the predominant type. Many surgeons prefer 2-phase esophagectomy (Lewis Tanner approach) for mid and lower third tumors. The stomach is first prepared via the abdomen. This is followed by a right thoracotomy when the esophageal tumor and relevant draining lymphatics are resected. The gastric conduit is then brought to the chest for esophagogastric anastomosis near the apex of the thoracic cavity. For lower third or GEJ tumors, a left thoracoabdominal approach or a single left thoracotomy incision with diaphragmatic incision are alternatives. The transhiatal approach is more suitable for distally located tumors with anastomosis in the neck. For Siewert type II or III GEJ tumors, the lower mediastinum can be accessed by widely opening the hiatus, and this can be achieved by dividing the crus laterally and the diaphragm anteriorly. The lower esophagus can then be transected. Anastomosis is more easily constructed by using a mechanical stapler. When the proximal stomach is involved and a total gastrectomy is required, the reconstruction is then performed in Roux-en-Y manner in the lower mediastinum.

**Transthoracic Esophagectomy (TTE) Versus Transhiatal Esophagectomy (THE).** This debate between TTE and THE remains controversial. THE avoids a thoracotomy at the expense of a thorough mediastinal lymphadenectomy, in particular the middle and superior mediastinum. Both approaches have advocates. Randomized controlled trials in the 1990s failed to demonstrate the superiority of either approach, and the main criticism was that these trials were too small to demonstrate significant differences. The largest randomized controlled trial to date compared 106 patients who
underwent THE and 114 patients who underwent TTE for mid-lower third/cardia adenocarcinoma. Pulmonary complication rates were 27% for THE and 57% for TTE. The THE group had longer ventilation time, intensive care unit stay, and hospital stay. In-hospital mortality and overall 5-year survival rates were similar in both groups. Patients who underwent TTE had more lymph nodes harvested (31 vs 16). In those with 1 to 8 positive lymph nodes, TTE had a survival advantage (64% vs 23% at 5 years). However, survival rates were similar in patients without nodal metastases or with more than 8 nodal metastases.83

In choosing TTE or THE, there are several factors to consider, including the location and stage of the tumor, neoadjuvant treatment, and the intended extent of the lymphadenectomy. For upper or middle third tumors or advanced tumors closely related to the tracheobronchial tree, in patients who have had prior chemoradiation where tissue planes may have been obliterated, the THE approach may not be safe. However, THE can be more safely performed for distally located tumors where dissection can be performed under visual control. Oncologically, if extended nodal dissection is planned for the middle and superior mediastinum, THE would not be suitable, and this is only possible with TTE.

**Minimally Invasive Esophagectomy (MIE).** Cuschieri and colleague first reported esophagectomy using video-assisted thoracoscopic surgery (VATS) in 5 patients in 1992.84 Since then, various combinations of minimally invasive techniques for esophagectomy have developed. The most popular approach is the combination of thoracoscopy and laparoscopy. Other variations in methods include doing the thoracoscopic dissection in the left lateral or prone position and performing or not performing an intrathoracic or cervical anastomosis. VATS approach with intrathoracic anastomosis was reported in 1995.85 Recently, the application of robotic-assisted thoracoscopic and/or laparoscopic esophagectomy using the da Vinci system has also been reported.86

The superiority of MIE compared to open approach has been investigated. Meta-analyses have shown some benefits with the minimally invasive approach. In one study, 672 patients who underwent MIE were compared with 612 patients who underwent open esophagectomy. The MIE group had reduced blood loss, less respiratory complications, shorter hospital stay, and lower morbidity rates.87 The only multicenter randomized controlled trial of
MIE studied 59 patients who underwent MIE (combined thoracoscopy in prone position and laparoscopy) and 55 patients who underwent open esophagectomy. An almost 3-fold greater pulmonary complication rate was found with the open group, with no difference in mortality rate. Postoperative quality of life was also superior in the MIE group. Oncologically, the number of retrieved lymph nodes and short-term survival were similar between MIE and the open approach.

There are a limited number of reports on long-term outcome of MIE for esophageal cancer. A report from Japan that compared VATS esophagectomy versus open approach in historical cohorts found that there was no difference in 3- and 5-year survival between the 2 groups. The 5-year stage-specific survival after MIE was reported as follows: stage I, 85%; stage IIA, 33%; stage IIB, 37%; and stage III, 16% (AJCC staging system sixth edition). Despite the better short-term outcome of MIE, the oncologic benefit of MIE has not been proven because there has been no large-scale randomized controlled trial to verify the benefit. Conducting randomized controlled trials for esophageal cancer, especially involving MIE, was once believed to be difficult because of the small number of patients in each single institute, heterogenous surgical technique or lack of expertise to execute the procedure, and other reasons. Recently, a study group composed of 17 institutions conducted a prospective phase II trial (Eastern Cooperative Oncology Group [ECOG] 2202) to verify the feasibility of total MIE (total thoracoscopic or laparoscopic esophagectomy and esophagogastric anastomosis in the neck). A total of 95 patients underwent MIE. Anastomotic leak occurred in 8.6% of patients, acute respiratory distress syndrome in 5.7%, pneumonitis in 3.8%, and atrial fibrillation in 2.9%; the 30-day mortality rate was 2.1%; and the 3-year overall survival was 58.4%. These results are comparable to that of open approach. Minimally invasive esophagectomy has become the standard of care at many institutions around the globe. Most reported similar, if not better, results compared with open surgery.

**Extent of Resection.** Curative (R0) resection in esophagectomy entails clear resection margins, including proximal, distal, and adventitial margins for the primary tumor, and radical clearance of the lymphatic drainage systems. Due to the differences in location between SCC and adenocarcinoma and to a certain extent their biologic behavior, the extent of lymphadenectomy performed is often different for the 2 cell types.
**Resection Margins of the Primary Tumor.** Esophageal cancer has a tendency to spread longitudinally. Studies have shown that the prevalence of intraepithelial and intramural spread could be as high as 46% and 53%, respectively, with multiplicity of tumor in 30% of patients. The deeper the invasion of the primary tumor, the more likely this spread will happen. The chance of finding tumor histologically at the resection margin and also subsequent recurrence at the anastomosis is reduced with increasing length of the transected esophagus away from the primary tumor. An axial in situ margin of 10 cm (fresh contracted specimen of about 5 cm) is advocated, which leads to a less than 5% chance of anastomotic recurrence. Intraoperative frozen section is one method to ensure a negative margin, although this does not guarantee absence of anastomotic recurrence later. In our experience, 7.5% of patients had a positive resection margin, 10.3% of whom developed anastomotic recurrence compared to 4.9% of patients with a negative margin.

Positive adventitial margin increases local recurrence rate and jeopardize survival. However, achieving a clear adventitial margin is difficult in esophagectomy because of the close relationship between the esophagus and adjacent indispensable organs. Neoadjuvant chemoradiation is increasingly being used to downstage tumor and increases the probability of R0 resection. En bloc resection is advocated in some centers and entails resection of the primary tumor together with the pericardium, thoracic duct, azygos vein, intercostal vessels, and bilateral pleurae overlying the primary tumor and a surrounding cuff of crura. This approach, however, may not be applicable to middle or upper third tumors due to the proximity of the tracheobronchial tree and is more suitable for adenocarcinomas of the lower esophagus.

**Extent of Lymphadenectomy: Squamous Cell Cancers** The ability to perform lymphadenectomy is closely related to the surgical approach used. Lymphadenectomy for SCC is performed by transthoracic approach, either open or minimally invasive, unless only a limited lower mediastinal dissection is planned. In countries where SCCs are prevalent, transhiatal resection is uncommonly performed based on safety concerns and because the value of lymphadenectomy is less questioned. Evidence is accumulating in advocating extended lymphadenectomy. However, the risks and benefits must be balanced with the increased extent of the surgical procedure.

Different extents of lymphadenectomy for SCC have been described. The
nomenclature of mediastinal lymphadenectomy was standardized in the 1990s, although the terms are not widely adopted and are often misused. Standard 2-field lymphadenectomy involves dissection of the infracarinal lymphatic drainage system and lymph nodes around the celiac trifurcation. When additional superior mediastinal nodal dissection along the right paratracheal area and right recurrent laryngeal nerve is performed, it is called extended 2-field lymphadenectomy. If the lymphatic chain along the left recurrent laryngeal nerve is also resected, it is regarded as complete 2-field lymphadenectomy. The addition of bilateral cervical lymph node dissection is regarded as 3-field lymphadenectomy (Figs 26-10 to 26-15). For intrathoracic SCCs, detailed lymph node mapping of metastatic disease in Japan shows that lymph nodes can spread to the neck, mediastinum, and upper abdomen around the celiac trifurcation. The overall rate of cervical lymph node metastases is approximately 30%. In relation to the level of primary tumor, cervical lymph nodes are involved in 60%, 20%, and 12.5% of upper, middle, and lower third tumors, respectively. When nodes along the recurrent laryngeal nerves from the superior mediastinum are considered together with the cervical nodes as 1 entity, the “cervicothoracic” group nodes are involved in up to 63.4% of proximal third, 45.2% of middle third, and 42.0% of lower third cancers. These data provide the rationale behind “3-field” lymphadenectomy, where the true value of extended lymphadenectomy does not lie with the addition of a cervical phase, but the completeness of the superior mediastinal dissection along the recurrent laryngeal nerves to the neck.
FIGURE 26-10 The extent of mediastinal lymphadenectomy: A. Standard mediastinal lymphadenectomy includes removing the paraesophageal nodes and subcarinal and right and left bronchial nodes below the tracheal bifurcation. B. Extended mediastinal lymphadenectomy involves standard lymphadenectomy plus right apical nodes, right recurrent laryngeal nerve nodes, and right paratracheal nodes. C. Total mediastinal lymphadenectomy includes an extended mediastinal lymphadenectomy plus the left recurrent laryngeal and paratracheal nodes.

FIGURE 26-11 Infracarinal mediastinal dissection. A, aorta; C, carinal lymph node on esophagus; E, esophageal portable; LMB, left main bronchus; P, pericardium; RMB, right main bronchus; T, trachea.
FIGURE 26-12 Superior mediastinal dissection. Large metal retractor retracting the trachea anteriorly to expose the left recurrent laryngeal nerve (LRN). A, aortic arch; E, esophagus; LMB, left main bronchus; RBA, right bronchial artery, which is preserved; RMB, right main bronchus; T, trachea.
FIGURE 26-13  Right recurrent laryngeal nerve node dissection. RRN, right recurrent laryngeal nerve; SA, subclavian artery; T, trachea; V, vagus nerve.

FIGURE 26-14  Abdominal lymphadenectomy involves dissection around the coeliac trifurcation. HA, hepatic artery; LG, left gastric artery stump.
ligated; SA, splenic artery.

FIGURE 26-15 For cervical lymphadenectomy, the cranial landmark is the cricoid cartilage and the caudal border is the upper margin of the clavicle. The most important nodes are the paratracheal nodes along the recurrent laryngeal nerves. Left neck dissection. CA, carotid artery; E, esophagus; IJV, internal jugular vein; LRN, left recurrent laryngeal nerve; S, stomach; T, trachea. The esophagogastric anastomosis is seen. Constructed with a 1-layer continuous suturing technique.

Three-field lymphadenectomy as practiced in Japan shows an overall hospital mortality rate of 4%. Although this very low mortality rate is achieved, most of these results come from experienced and specialized institutions, and such extensive surgery is expected to carry with it a more unfavorable outcome if it is more widely and unselectively applied. In addition, morbidity rates are substantial; septic complications were the most common at 26.8%, followed by pulmonary complications (21.3%). Recurrent laryngeal nerve injury can occur in more than 50% of patients, which
predisposes to pulmonary complications and impairs long-term quality of life.\textsuperscript{97}

The realization that an extensive operation can result in substantial morbidity and that not all patients will benefit has driven the recent focus of research to further refine the indications for extended lymphadenectomy. A recent study evaluated an efficacy index (EI), which is defined as the incidence of metastasis to a region (\%), multiplied by the 5-year survival rate (\%) of patients with metastasis to that region, and then divided by 100. This is an assumptive figure, expressing the possible effect of dissection of a certain lymph node region to increase the 5-year survival rate of the whole group. It was found that cervical lymphadenectomy had a high EI for upper and middle third tumors but a low EI for lower third tumors.\textsuperscript{98} Similarly, abdominal nodal dissection may not be beneficial for upper third tumors. In patients with demonstrable recurrent laryngeal lymph nodes preoperatively, cervical nodal dissection may be worthwhile even for lower third tumors. However, in patients without such nodes, cervical nodal dissection may not have a survival advantage. Other strategies include using intraoperative polymerase chain reaction to examine recurrent laryngeal nerve lymph nodes to predict the need for cervical dissection, similar to the concept of sentinel lymph node metastasis, and taking a 2-stage operative approach to select patients suitable for cervical lymphadenectomy. Replacing 3-field lymphadenectomy with neoadjuvant, adjuvant, or intraoperative radiotherapy is an alternative, but the role of radiotherapy remains controversial.

\textbf{Extent of Lymphadenectomy: Barrett Adenocarcinoma and Gastric Cardia Cancers.} The lymphatic spreading behavior of Barrett adenocarcinoma and gastric cardia is different from SCC. Positive nodes are found in approximately 10\% of patients with SCCs for T1a lesions, whereas in Barrett adenocarcinoma, this rate is only 0\% to 6\%. In T1b cancers, the respective figures are 30\% to 50\% for SCCs and 20\% for adenocarcinomas. In addition, the pattern of lymphatic spread also differs; more than 85\% of all positive nodes in early adenocarcinoma are located in close proximity to the primary tumor, in contrast to less than 60\% in SCC.\textsuperscript{99} Nodes are not commonly found in the superior mediastinum and, when present, probably indicate very widespread disease. Thus, lymphadenectomy is generally performed using a standard 2-field approach. The advent of transhiatal esophagectomy came at a time when esophagectomy was a high-risk operation with high mortality
rates, and this less invasive method probably contributed to reducing overall death rates. With improvement in surgical techniques and perioperative care, it seems that, in most experienced centers, when selected appropriately, both procedures can be carried out safely and the margin of benefit in reducing morbidity for most patients with the transhiatal operation is not overwhelming. In addition, more evidence has accumulated in recent years showing the benefits of radical lymphadenectomy.

Logan and Skinner et al first introduced the concept of en bloc resection for esophageal cancer. In en bloc resection, the thoracic esophagus is resected together with a fascial cylinder enclosing the tumor-bearing zone of the esophagus and the lymphatic drainage system. The structures for resection include the primary tumor, azygos vein, thoracic duct, pericardium, intercostal vessels and bilateral mediastinal pleurae. This approach increases clearance of the lateral margin and is most suitable for adenocarcinoma because of its tumor location. En bloc resection is less applicable for SCC, since most SCCs are located adjacent to the trachea-bronchial tree where extension of this lateral margin is not possible.

Excellent results are reported for en bloc resection in appropriately selected patients; a morbidity rate of 40%, mortality rate of less than 5%, and 5-year survival rate of 37% to 52% have been reported in dedicated centers. Tumor recurrence rate was investigated in patients who underwent en bloc resection. The local recurrence rate is less than 5% within the field of dissection, and if nodal recurrence develops, it is mostly found outside the dissection field.

For tumors of the gastric cardia (Siewert type II and III tumors), most surgeons would perform a total gastrectomy with a Roux-en-Y jejunal loop reconstruction, although some would prefer to preserve the distal stomach for anastomosis. An upper abdominal compartment nodal dissection around the celiac axis seems routine for all, but complete lower mediastinal nodal dissection is somewhat controversial. Some argue that thorough lower mediastinal dissection is needed, and this is only possible with the addition of a thoracotomy. Others believe that this is unnecessary, and mediastinal nodal involvement could indicate advanced disease for which survival is poor regardless of the extent of lymphadenectomy. The Japanese Oncology Group trial 9502 addressed this question. Patients whose tumors were Siewert II or III adenocarcinomas and that infiltrated into the esophagus for less than 3 cm were randomly assigned to a transabdominal (n = 82) or left
thoracoabdominal approach (n = 85). A more thorough mediastinal dissection was deemed only possible with the later approach. The trial was closed prematurely after the first interim analysis, when the predicted probability of the left thoracoabdominal approach having a significantly better overall survival than the transabdominal route at the final analysis was only 3.7%. The morbidity rate was worse after the left thoracoabdominal approach. Thus, a transabdominal approach seems adequate, but the surgeon must be prepared to add a thoracotomy when frozen section indicates a positive proximal resection margin.

Another pivotal trial is the Dutch trial comparing THE versus TTE for Siewert type I and II adenocarcinoma of the GEJ; the details have already been discussed earlier.\(^{105}\) For type I cancers, TTE with mediastinal lymphadenectomy may impart a survival advantage in patients with limited nodal metastases.

Regardless of histology, more data have emerged supporting the benefits of radical lymphadenectomy. An international multicenter study involving 2303 patients showed that presence of nodal metastases, number of nodes involved, and number of nodes removed were important prognostic factors in addition to depth of tumor invasion, age, sex, and histologic type. The number of nodes removed (reflection of the extent of lymphadenectomy) correlated with overall survival. The optimal number of nodes resected in this study was 23.\(^{106}\) The Worldwide Esophageal Cancer Collaboration (WECC) involving 4627 patients with either SCC or adenocarcinoma suggested the optimal number of nodes to be removed should be related to the pT stage: 10 for pT1 tumors, 20 for pT2, and 30 for pT3 or pT4.\(^{107}\)

**RECONSTRUCTION AFTER ESOPHAGECTOMY**

The reconstruction phase of an esophagectomy determines to a significant extent the postoperative morbidity and long-term quality of life. The main areas to consider in reconstruction are the choice of esophageal substitute and the route of reconstruction.

**Choice of Esophageal Substitute**
The most commonly used conduit is the gastric tube, and of the many configurations, an isoperistaltic tube based on the greater curvature with preservation of the right gastric and right gastroepiploic vessels is most reliable. The simplicity of preparation, adequate length, and robust blood supply make it the first choice as the esophageal substitute (Fig. 26-16). Disadvantages of the gastric conduit include the fact that patients who have an intrathoracic stomach often experience postprandial discomfort and early satiety related to loss of normal gastric functions such as receptive relaxation. Patients can also suffer from acid reflux, possible gastric ulceration, and dysfunctional propulsion. The level of the esophagogastric anastomosis has a bearing on the severity of reflux. Patients who have a low intrathoracic anastomosis tend to have more severe reflux and esophagitis compared with the high intrathoracic or cervical anastomosis. Preserving a longer length of esophagus, on the other hand, theoretically may enhance swallowing function. Inadequate gastric emptying can be a problem. A pyloric drainage procedure is not universally practiced. In a randomized trial, 13% of patients who did not have a pyloroplasty had problems with gastric emptying. A meta-analysis suggested that a drainage procedure lessens the chance of early postoperative gastric stasis, but long-term function is not affected.
Many other factors contribute to emptying of the intrathoracic gastric conduit. A smaller stomach enhances postoperative emptying. The straighter
position of the stomach, when delivered to the neck via the posterior mediastinal or the retrosternal route, may make the stomach empty more efficiently compared to one placed in the right pleural cavity, where the angulation at the diaphragmatic hiatus as the stomach continues from the right paravertebral gutter into the abdomen may produce relative obstruction. Rotation of the stomach at the hiatus should be avoided. With a gastric conduit, diet modifications and the use of acid suppressive and prokinetic drugs such as erythromycin may be useful.

There are instances when the stomach cannot be used, such as after previous gastric resection, and tumor involvement of a substantial part of the stomach dictating its removal. In these situations, the use of the colon is preferred. For most, colonic interposition remains an infrequently performed procedure and has the potential for more complications. Mobilization of the colonic loop is more complex; its blood supply is less reliable than the gastric conduit; 3 anastomoses are required; and when the colon becomes ischemic, the choice of alternative conduit is restricted. In our experience, use of a colon loop is associated with more blood loss, a longer operating time, and a higher anastomotic leak rate. Colon ischemia occurs in 1 of 42 patients (2.4%), which compares favorably to a rate of 3% to 10% reported in the literature.\textsuperscript{110}

A colonic conduit provides good long-term swallowing function; it seems to have active peristalsis, and this is cited as an explanation for its superior function as an esophageal substitute when compared with a passive gastric conduit. Although peristalsis can be demonstrated immediately following surgery, long-term emptying likely relies on gravity. When the distal stomach is retained in the abdomen after a colon interposition with a cologastric anastomosis, the latter provides additional reservoir function. A recently published study demonstrated that the colon could be used as the first choice for esophageal substitute with acceptable outcomes when compared to using the stomach and also avoids the problem of acid reflux. The stomach is preserved for its reservoir function.\textsuperscript{111}

The jejunum is used most frequently after distal esophagectomy and total gastrectomy for cancer of the lower esophagus and gastric cardia. A Roux-en-Y configuration seems best, as it prevents bile reflux to the esophagus. A jejunal loop used in a modified Merendino procedure to interpose between the esophagus and proximal stomach after limited resection of the distal esophagus and GEJ has also been advocated.\textsuperscript{112} Excellent postoperative
quality of life and function are claimed. A long jejunal loop is sometimes used to reach the neck, but preparation is tedious and the vasculature may not be reliable; a “supercharge” using a microvascular anastomosis to cervical vessels may be required. A free jejunal graft is used for reconstructing the defect after resection of the pharyngoesophageal segment in the neck, as previously discussed (Fig. 26-9).

**Route of Reconstruction**

The method of reconstruction is in part related to the surgical approach for resection. When a cervical anastomosis is chosen, one must decide whether to place the conduit via the orthotopic, retrosternal, or subcutaneous route. The subcutaneous route is rarely used because it is cosmetically unsightly. The retrosternal route was shown to be associated with increased or similar cardiopulmonary morbidity and mortality rates. The retrosternal route is 2 to 3 cm longer compared to the orthotopic route, but this is rarely of relevance because the esophageal replacement conduit is usually of sufficient length. Some suggest that the tight space at the thoracic inlet in the neck could cause potential constriction on the conduit and recommend partial manubrial, clavicular head, and first rib resection; we have found this unnecessary. Functionally, although it was shown that there is a higher rate of gastric retention when the retrosternal route is used, quality of life is not adversely affected. The orthotopic route of reconstruction may maintain better nutritional status than the retrosternal route.

When palliative resection is carried out for advanced tumor, recurrent tumor could infiltrate into the conduit placed in the posterior mediastinum. In a retrospective study of 209 patients who had undergone curative resection and orthotopic reconstruction, of 73 patients (35%) who had locoregional tumor recurrence, 46 (22%) had secondary dysphagia as a result. The authors concluded that in 27 patients (13%) dysphagia would likely have been prevented by using a retrosternal reconstruction route. However, the site of the obstruction that produced dysphagia was not clearly stated. The stomach is usually spacious, and tumor infiltration will not readily result in dysphagia. Only at the thoracic inlet and in the cervical region, where there is limited space, can tumor involvement lead to obstruction. Using the retrosternal route will eliminate tumor involvement in the posterior mediastinum, but
infiltration from tumors in the neck cannot be avoided. The benefits of choosing the retrosternal route in reducing secondary dysphagia from recurrent tumor infiltration may be overemphasized. In our own study, only 4 (14%) of 28 patients developed tumor infiltration into the gastric conduit in the posterior mediastinum. The main symptom was bleeding in 2 patients, and none had dysphagia. Therefore, it is our policy to only use the retrosternal route for reconstruction when resection is palliative, especially when postoperative radiotherapy is planned, or when the reconstructive phase of the operation precedes tumor resection.

**PERIOPERATIVE CARE AND POSTOPERATIVE MORBIDITY AND MORTALITY**

Esophagectomy mortality has significantly improved in the past 3 decades, but it is still a major procedure with risk. In the West, the mortality rate is between 7% and 9%, and the overall complication rate ranges from 17% to 74%. With adequate preoperative workup, however, serious cardiac events like myocardial infarction should be rare. Atrial arrhythmia is common, affecting about 20% of patients. In itself, atrial fibrillation is benign, but it serves as a marker for more serious underlying pulmonary and septic surgical complications. Occurrence of atrial arrhythmia should prompt thorough search for a more ominous underlying cause.

Pulmonary complications remain the most common and serious postoperative morbidity. Major complications can affect 30% of patients; most series report a rate of about 20%. Pneumonia and respiratory failure occurred in 15.9% of our patients and were responsible for 55% of hospital deaths. Predictive factors include advanced age, supracarinal tumor location (in part related to recurrent laryngeal nerve injury), and lengthy operating time. Neoadjuvant therapy did not lead to increased morbidity. Measures to improve respiratory outcome include cessation of smoking preoperatively, chest physiotherapy, avoidance of recurrent laryngeal nerve injury, cautious fluid administration to avoid fluid overload, use of smaller chest tubes, early ambulation, regular bronchoscopy, and early tracheostomy for sputum retention. Epidural analgesia is invaluable in postoperative pain relief and
has been shown to improve outcomes.\(^{122}\)

The most common surgical complication after esophagectomy is anastomotic leak. A leak rate of below 5% can be achieved in dedicated centers.\(^{123}\) Most leaks are probably related to technical errors, such as tension between the conduit and the esophageal stump, ischemia of the conduit as a result of rough handling and poor preparation, and suboptimal technique. The intrinsic vascular perfusion of the stomach can be enhanced by certain methods, such as “ischemic preconditioning,” whereby partial mobilization of the gastric conduit is later followed by a second-stage anastomosis.\(^{124}\) The perfusion of the stomach could be shown to improve in the interim period. Although an interesting concept and potentially useful, the existing wide range of reported leak rates (from 2%-3% to 30%) suggests that much improvement is possible by other means, even without ischemic conditioning.

A recently devised technique to assess conduit perfusion intraoperatively is laser-assisted fluorescence. Indocyanine green is injected intravenously, and angiography of the substitute is evaluated. A recently published study on 144 patients who underwent esophagogastric anastomosis showed that the leak rate was significantly less when the anastomosis was performed at the site of robust blood perfusion compared to a site that was less well perfused (2% vs 45%).\(^{125}\)

The actual method of anastomosis is perhaps less important than its proper application. Stapled anastomosis is popular for intrathoracic anastomosis, whereas the hand-sewn technique is preferred in the neck. There is no evidence from randomized trials that leak rates differ between stapled and hand-sewn anastomoses, but the circular stapler may give rise to more strictures.\(^{126}\) The linear stapler has also been advocated in the neck. One group reduced their cervical leak rate from 10% to 15% using a hand-sewn technique to 2.7% using linear staples with a side-to-side anastomosis.\(^{127}\) With experience, however, the hand-sewn method is as safe, if not more so, and certainly less expensive.

As mentioned already, technical variables play an important role in the genesis of postoperative complications. Anastomotic leaks (largely technical) and recurrent laryngeal nerve injury, for instance, are related to higher incidences of postoperative pulmonary morbidities. At the author’s center, pulmonary complications occurred in 10% of patients without technical complications and in 38% of patients who developed such morbidities, and
mortality rates were 3.3% and 9.2%, respectively. Multivariate analyses also demonstrated that a long operating time is related to pulmonary complications, and increasing intraoperative blood loss is related to postoperative mortality. In sum, the meticulous and expeditious execution of an esophagectomy and its subsequent reconstruction are of paramount importance in lessening complication and mortality rates.

Vigilant and aggressive treatment of complications is important for good outcomes. Management of complications has improved with time. At the author’s unit, the anastomotic leak rate was 16% in the 1960s to 1970s; 61% of these patients died, resulting in a leak-related mortality of 9.8%. In the 1980s, the leak rate was 3.5%, and 35% of these patients died, for a leak-related mortality of 1.2%, whereas in the late 1990s, leak occurred in 3.2% of patients and none died as a result. Leak rate has remained similar since.

Other surgical complications such as chylothorax and herniation of bowel through the diaphragmatic hiatus are rare but should be recognized early; both are corrected by surgical reexploration.

**Standardization of the Definition of Perioperative Complications**

Variation in institutional practice may contribute to different outcomes. A recently published study shows that there is significant interinstitutional heterogeneity with regard to reporting of postesophagectomy complications. Another study identified 210 different complications in 98 publications, more than 60% of which did not specifically define the reported complications. A review of esophageal outcomes from 164 National Surgical Quality Improvement Project (NSQIP) hospitals in the United States demonstrated that operative results between centers varied by 161% for 30-day mortality and 84% for major morbidity. To resolve this issue, an international consensus on standardization of data collection and definitions for complications of esophagectomy with participation of 13 countries has been launched. Consistency in definitions of complications and survival allows more meaningful and accurate comparison of outcomes between centers and will possibly improve the quality of care in the future.
MULTIMODALITY TREATMENT STRATEGIES

The past 3 decades have seen a proliferation of additional treatments for esophageal cancer. The rationale is based on the suboptimal long-term results of surgery or radiotherapy. Both the spatial and synergistic actions of chemotherapeutic agents and radiotherapy are explored in multimodality treatments. How surgical resection and these new combinations should be integrated into treatment programs is an active area of research.

Neoadjuvant Radiotherapy

Neoadjuvant radiotherapy has not been shown to increase resection rate or improve survival when compared with surgery alone. The European Organization for Research and Treatment of Cancer (EORTC) study suggested improved local disease control but no better long-term outcome.\textsuperscript{132} A Cochrane meta-analysis showed that if preoperative radiotherapy regimens do improve survival, the effect is likely to be modest, with an absolute survival benefit of 3% at 2 years and 4% at 5 years that was not statistically significant ($P = .062$).\textsuperscript{133}

Adjuvant Radiotherapy

The largest randomized controlled trial on adjuvant radiotherapy recruited 495 patients with intrathoracic SCCs for analysis. Postoperative radiotherapy of 50 to 60 Gy was given in 220 patients to the entire mediastinum and bilateral supraclavicular fossae. Per-protocol analysis showed no overall difference in 5-year survival, which was 31.7% for the surgery-alone group and 41.3% for the radiotherapy group. A benefit in the radiotherapy group was observed in stage III patients; 5-year survival rates were 13.1% and 35.1%, respectively. In patients with node-positive disease, the difference in survival was of borderline significance. The chance of mediastinal, cervical lymph node, and anastomotic recurrence was also reduced.\textsuperscript{134} Survival benefit was not demonstrated for the other trials. Postoperative radiotherapy may be beneficial to subgroups of patients, especially those who have palliative resections, to enhance local disease control.
Neoadjuvant Chemotherapy

The role of preoperative chemotherapy was studied extensively. The 2 largest trials were the Intergroup (INT 0113) trial in the United States and the Medical Research Council (MRC) (OE02) trial in the United Kingdom. The first study randomized patients to undergo surgery alone or to have 3 cycles of cisplatin and fluorouracil before surgery and, in those who had stable or responsive disease, 2 additional postoperative courses. Of 440 eligible patients, 213 were assigned to the neoadjuvant group. The median survival was 14.9 months for the chemotherapy group compared with 16.1 months for the surgery group. Two-year survival rates were no different at 35% and 37%, respectively. The MRC trial (OE02) involved 802 patients and similar preoperative regimens with 2 courses of cisplatin and fluorouracil. Overall survival was better in the chemotherapy group. Median survival was 16.8 months versus 13.3 months, and 2-year survival rates were 43% and 34%. The long-term follow-up data have been reported; with a median follow-up of 6 years and 93% of patients followed to 5 years or death, 5-year survival rates were 23% in the chemotherapy group compared with 17% in the surgery group. Benefits were evident for both SCC and adenocarcinoma.

Many differences between the 2 studies could explain the different outcomes, including the chemotherapy regimen, distribution of histologic cell types (66% adenocarcinoma in the MRC trial and 54% in the INT trial), the number of patients who underwent resection, time to resection, type of surgery performed, and number of patients who also had radiotherapy. The larger sample size in the MRC trial also could have facilitated the detection of a small improvement with chemotherapy.

A Japanese study conducted by the Japanese Clinical Oncology Group (JCOG 9907) randomized 330 patients with stage II or III SCCs (excluding T4 disease) to either 2 courses of preoperative cisplatin and fluorouracil or a similar regimen given after esophagectomy. Overall 5-year survival was significantly better at 60% in the preoperative chemotherapy group compared to 38% in the postoperative group. Although this trial did not specifically compare preoperative chemotherapy to surgical resection alone, this has quickly become a standard-of-care treatment in Japan. In the United Kingdom, the MRC OE02 trial has also established preoperative chemotherapy as a widely practiced strategy.
OE05 compares the OE02 preoperative chemotherapy regimen (2 cycles of cisplatin and fluorouracil [CF]) to 4 courses of preoperative epirubicin, cisplatin, and capecitabine (ECX) in patients with adenocarcinoma of the esophagus and GEJ (Siewert type I and II; note that OE02 involved both SCC and adenocarcinoma), followed by esophagectomy with 2-field lymphadenectomy. From 2005 to 2011, 897 patients (CF, n = 451; ECX, n = 446) from 72 centers were randomized. ECX resulted in more toxicities, but postoperative complications and mortality rates were similar (90-day mortality rates were 4% for CF and 5% for ECX). Progression-free survival and disease-free survival favored ECX, but statistically, they were not significantly different; same was true for overall survival. Three-year survival rates were 39% for CF and 42% for ECX.139

The MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, a randomized study, included 503 patients with adenocarcinoma of the stomach, GEJ, and lower esophagus. Initially planned for gastric cancers, eligibility criteria were extended to include lower esophageal adenocarcinoma coinciding with termination of OE02. Thus, 14% of patients had lower esophageal tumors, and another 12% had GEJ tumors. Three courses of epirubicin, cisplatin, and infused fluorouracil (ECF) were given to patients before surgery, and 3 courses were repeated afterward; patient who received this regimen were compared to patients who underwent surgical resection alone. Both progression-free and overall survival rates were improved in the chemotherapy group.140

**Adjuvant Chemotherapy**

This is an area perhaps least well studied, and trials on pure postoperative chemotherapy are limited. JCOG 9907, mentioned in the previous section, was in fact a follow-up study on JCOG 9204, which randomized 242 patients comparing surgical resection with and without the addition of 2 courses of postoperative cisplatin and fluorouracil. The 5-year disease-free survival rate was significantly different between the groups (45% with surgery alone and 55% with surgery plus chemotherapy). The overall 5-year survival rates were not significantly different, at 52% and 61%, respectively. The effect was more marked in the subgroup with lymph node metastases.141
Neoadjuvant Chemoradiation

The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial randomized 366 patients to chemoradiotherapy followed by surgery (n = 178) versus surgery alone (n = 188). It was shown that neoadjuvant chemoradiotherapy did not increase morbidity and the hospital mortality rate. The neoadjuvant chemoradiotherapy group had a significantly better median survival of 49.4 months versus 24 months in the surgery-only group. The 5-year overall survival also favored neoadjuvant chemoradiotherapy plus surgery over surgery alone with a median of 45 months of follow-up. Seventy-five percent of the population in this study had adenocarcinoma, 23% had SCC, and 2% had large-cell undifferentiated carcinoma. On subgroup analysis, neoadjuvant chemoradiotherapy for adenocarcinoma had a better survival than surgery alone, and similar findings were identified for SCC. The long-term follow-up (a minimum of 5 years) results demonstrated that the median overall survival for patients with SCC was 81.6 months in the neoadjuvant chemoradiotherapy plus surgery group and 21.1 months in the surgery-alone group. For adenocarcinoma, the survival time was 43.2 months in the neoadjuvant chemoradiotherapy plus surgery group and 27.1 months in the surgery-alone group.

Walsh and colleagues investigated neoadjuvant chemoradiation for adenocarcinomas only, but the trial was criticized for inadequate preoperative staging, unclear surgical procedures, and a large number of protocol violations, and survival from the surgery group was exceptionally poor (3-year survival rates were 32% and 6% for the preoperative treatment group versus surgery-alone group, respectively).

Although it cannot be said conclusively that neoadjuvant chemoradiotherapy is superior to surgery alone in the treatment of localized esophageal cancer, it is widely practiced, especially in the United States. Neoadjuvant chemoradiotherapy does result in more pathologic complete responses compared with chemotherapy (25%-30% vs <10%). One trial compared preoperative chemotherapy with preoperative chemoradiation therapy in advanced adenocarcinoma of the lower esophagus and GEJ. More pathologic complete responses were observed in the chemoradiation group (16% vs 2%), and more patients had negative nodal involvement (64% vs 38%). A trend toward improved median survival (32.8 vs 21.1 months) and 3-year survival (47.4% vs 27.7%) was also seen, although these results did
Definitive Chemoradiation

The Radiation Therapy Oncology Group (RTOG 85-01) trial of chemoradiation versus radiotherapy provided convincing evidence of the superiority of chemoradiation. The 5-year survival rate reported for the combined therapy group was 26% compared to 0% after radiotherapy (median survival, 14 vs 9 months). Data on recurrence patterns showed that both local and distant disease control were superior with combined treatment. Local persistence of disease and recurrence rates were 47% for chemoradiotherapy and 65% for radiotherapy. Intensification of radiation dose to beyond 50.4 Gy did not yield further advantage but potentially added complications.

A Cochrane meta-analysis on 13 randomized trials that compared chemoradiation with radiation confirmed the superiority of chemoradiation. Concurrent chemoradiation provides a significant overall reduction in mortality at 1 to 2 years, an absolute reduction in death rate by 7%, and a reduction in local persistence/recurrence rate by 12%. The downside is a 17% increase in grade 3 and 4 toxicities. Sequential chemoradiation provides no benefit, perhaps demonstrating the need to maximize the radiosensitizing properties of chemotherapy.

The Role of Surgery

The RTOG trial suggested that, in patients with T1-3N0-1M0 disease, a 14% to 26% 5-year survival can be expected. It has been suggested that surgery may be of no additional value to chemoradiation and should be relegated to use as an adjuvant treatment.

Two clinical trials attempted to examine whether surgical resection was necessary after chemoradiation. A French study (FFCD 9102) treated 444 patients with both SCCs and adenocarcinomas of stage T3-4N0-1M0 with 2 cycles of flourouracil, cisplatin, and concurrent radiation (46 Gy at 2 Gy/d or split course of 15 Gy in weeks 1 and 3). Only 259 patients who had at least a partial response were randomized to undergo immediate surgery or to have 3 more cycles of chemotherapy with 20 Gy at 2 Gy/d or split-course 15 Gy.
The death rate within 3 months after starting induction treatment was 9% for the surgery group compared with 1% in the chemoradiation group. Two-year survival rates (34% and 40%) and median survival (17.7 and 19.3 months) were not significantly different between the surgical and nonsurgical groups, respectively. Patients in the surgical arm, however, required stenting less often (13% vs 27%) and fewer dilations (22% vs 32%). There was no difference in the long-term quality of life, but the surgery arm had transient deterioration in the immediate postoperative period.

A German multicenter trial recruited 172 patients with SCC (T3-4N0-1M0). Three cycles of fluorouracil/leucovorin/etoposide/cisplatin were given followed by chemoradiation (cisplatin/etoposide + 40 Gy). Resection was then performed. This was compared to a control group administered the same chemotherapy, followed by definitive chemoradiation (cisplatin/etoposide + >60 Gy). A nonsignificant trend toward better overall survival at 5 and 10 years was observed: 27.9% and 19.2% in the resection group, compared to 17.0% and 12.2% in the chemoradiation-alone group. Local tumor control was significantly worse in the nonsurgical arm. Three-year survival rate was 35% in nonresponders undergoing complete tumor resection compared to 11% in nonresponders who did not undergo resection. Both the French and German studies concluded that surgical resection may not be necessary after chemoradiation therapy.

It may be premature to negate the value of surgical resection. First, chemoradiation is by no means harmless, and surgical resection may not be as morbid as described. Treatment duration of chemoradiation is often long, and compliance is problematic. Only 68% of the patients in the RTOG 85-01 trial could complete the planned treatment. In the control arm of INT 0123, acute grades 3 and 4 toxicity affected 43% and 26% of patients, respectively, and long-term grades 3 and 4 toxicity affected 24% and 13% of patients, respectively. Treatment-related mortality was 5% to 9%, as reported by the INT trials. In studies that showed a benefit for chemoradiation or questioned the value of surgical resection, the results of the surgical arm were often suboptimal. In the FFCD 9102 trial, the death rate within 3 months in the surgical arm was 9% compared to 1% in the nonsurgical arm; in the German trial, the mortality rates were 10% and 3.5%, respectively. The early surgical deaths likely biased the long-term survival results. Comparisons with nonoperative treatments will only be valid
when better results from high-volume centers are integrated into clinical trials.

Second, local disease control with chemoradiation alone is less than satisfactory. It can be shown that with increasing extent of lymphadenectomy, better local control is achieved with surgery; by comparison, nonoperative chemoradiation has a much higher local persistence/recurrence rate of over 50%.\textsuperscript{147} The relief of dysphagia, the main symptom requiring palliation, is much more certain with surgical resection; the need to treat dysphagia with a stent occurred twice as often in the nonsurgical group in the FFCD 9102 trial.\textsuperscript{149}

Third, residual disease exists for the majority of patients treated by chemoradiation. The pathologic complete response rate for most trials is in the region of 25% to 30%. Thus, it is logical to assume that surgical resection would enhance cure at least in the remaining 70% to 75% of patients who did not completely respond. In the German trial, the 3-year survival of nonresponding patients who underwent resection was 35% compared with 11% in those who did not.\textsuperscript{152} In the FFCD 9102 trial, 192 patients were not randomized primarily because of lack of objective response but also because of medical contraindications or patient refusal. Of these, 112 patients had operations; among these patients, 80 had R0 resection (42%). The median survival for the patients who underwent surgery was 17.3 months, compared with 6.1 months for those who did not, and was comparable for those who were randomized. The data suggest that salvage surgery could benefit a subset of patients who do not respond to initial therapy.\textsuperscript{153} Conversely, the role of surgery is less obvious in those with a complete response. However, ascertaining true complete response is difficult. Recent studies using fluorodeoxyglucose positron emission tomography (PET) scans show promise; however, although PET scan can more reliably distinguish responders and nonresponders, it is not accurate enough to pinpoint the complete pathologic responders.\textsuperscript{154}

The dilemma of when surgery can be omitted remains when faced with complete clinical response after multimodality treatment. An ongoing multicenter trial in France (Esostrate) attempts to compare immediate surgery versus surveillance and rescue surgery for recurrence in esophageal cancer with complete clinical response after chemoradiotherapy.\textsuperscript{155} Another equally important prerequisite element to answer the above question is the accuracy
of current diagnostic tools in defining real complete clinical response. A Dutch group proposed a study to test the accuracy of detecting residual disease after CROSS neoadjuvant chemoradiotherapy (Pre-SANO study). In this Pre-SANO study, two rounds of clinical response evaluations by endoscopy with biopsy and endoscopic ultrasonography with fine needle aspiration showed sensitivity and specificity for differentiation between tumor regression grade (TRG) 3-4 (residual viable cells >10%) and TRG 1 (no residual viable cell) were 90% and 72% respectively. Follow this trial, SANO, if diagnostic tests are indeed accurate, then the concept to test “surgery as needed” (for recurrence after complete clinical response) approach (SANO trial) will be appropriate. Much interest will be generated with the results of these studies.

**Prediction of Response and Response-Directed Therapy**

Reliable predictors for response to chemoradiation would be useful, because multimodality treatments are toxic, time consuming, and costly. Various markers have been explored, such as simple histology, proliferative cell nuclear antigen (PCNA), epidermal growth factor receptor (EGFR), Ki-67, cyclin D1, thymidylate synthase, and microvessel density, both in tissue and in serum. To date, none has been proven to help clinical decision making. Metabolic imaging with PET scan has some promise. The degree of response detected by PET imaging has been shown by many studies to correlate with pathologic response after chemotherapy or chemoradiotherapy (Fig. 26-17).
FIGURE 26-17  Positron emission tomography/computed tomography before (A) and after (B) chemoradiation therapy; the tumor has become completely eumetabolic.

The MUNICON (Metabolic Response Evaluation for Individualization of Neoadjuvant Chemotherapy in Oesophageal and Oesophagogastric Adenocarcinoma) trial evaluated patients with locally advanced adenocarcinoma of the distal esophagus or type II cardia tumors undergoing neoadjuvant chemotherapy. Early metabolic response was defined as a reduction of 35% or more in the mean glucose standard uptake value (SUV) measured by serial PET scans at the beginning and at 2 weeks after commencement of treatment. Responders continued chemotherapy for an additional 12 weeks before resection, whereas nonresponders went directly to immediate surgery. Of 119 patients, 110 were evaluable for metabolic responses, of whom 54 (49%) were responders. Significantly improved R0 resection rate (96% vs 74%), major pathologic response rate (defined as <10% residual tumor; 96% vs 0%), longer median event-free survival (29.7 vs 14.1 months), and longer median overall survival (median, not reached vs 25.8 months) were found for metabolic responders versus nonresponders. More importantly, the outcomes for nonresponders were not different from previous results in such patients who completed 3 months of chemotherapy, indicating that such a strategy did not compromise these patients and could save them from suboptimal chemotherapy.159
The same investigators reported on their MUNICON-2 trial. Metabolic nonresponders as defined in MUNICON were switched to chemoradiotherapy (both chemotherapy and chemoradiotherapy were cisplatin based). Of 32 patients recruited, 13 (41%) were metabolic nonresponders. Subtotal histologic response (<10% residual tumor) after chemoradiotherapy was reported in 3 patients (23%), but no complete response was observed. In contrast, the complete histologic response rate in metabolic responders was 16%. Higher rates of R1/2 resections were also observed for nonresponders (31% vs 16%). One-year progressive-free survival was also inferior (46% vs 63%). The study suggested that merely adding radiotherapy to the same cisplatin-based chemotherapy in nonresponders was only marginally better. Another strategy may be to switch to alternative, non–cross-resistant chemotherapy during radiation.\textsuperscript{160}

It seems that cisplatin- and fluorouracil-based chemoradiotherapy has reached its therapeutic limit in treating esophageal cancer. Paclitaxel has also become standard since the CROSS trial. More novel chemotherapeutic agents are being explored, including docetaxel, the topoisomerase I inhibitor irinotecan (CPT-11), vinorelbine, gemcitabine, Herceptin (trastuzumab), oxaliplatin, biomodulators such as interferon, and targeted therapies such as bevacizumab or cetuximab. This remains a very active area of research. In addition, advances in techniques in radiation delivery, such as intensity-modulated radiotherapy, may further reduce radiation toxicity.\textsuperscript{161}

One ongoing multicenter phase III Japanese trial compares 3 regimens of neoadjuvant therapy: cisplatin and fluorouracil versus docetaxel, cisplatin, and fluorouracil versus chemoradiotherapy with cisplatin and fluorouracil (JCOG 1109, NExT Study). Although this study does not specifically look at VATS esophagectomy, it will probably shed light on the safety and effects of such procedure in the neoadjuvant setting. Minimally invasive esophagectomy is allowed in this study, but surgeons need to be credentialed by a committee in order to take part, thus ensuring quality control of the surgical procedure. It would be interesting to see whether the results will be different with the open versus minimally invasive approach and after chemotherapy versus chemoradiotherapy. This study commenced in November 2012 and aimed at recruiting 501 patients in 6.25 years, with 2 interim analyses after enrolling half the number of patients.\textsuperscript{162}
PALLIATION

Endoscopic palliative treatments for more advanced tumors include placement of an esophageal prosthesis, laser therapy, intralesional injection of various substances, and PDT. The most commonly employed technique is perhaps insertion of a prosthesis, especially self-expanding metallic stents (SEMS; Fig. 26-18). The smaller diameter of the delivery mechanism makes aggressive dilation of the tumor before insertion unnecessary. These stents are more flexible than conventional plastic prostheses; membrane-covered versions have been developed to seal esophagoairway fistulae and prevent tumor ingrowth. Perforation, pneumonia, bleeding, and migration rates were significantly lower with metallic stents. Because of the lower morbidity, metallic stents were also more cost-effective despite their higher initial cost. The choice of various metallic stents depends on their individual characteristics, in terms of flexibility, tensile force, and degree of shortening on deployment in relation to the site of placement. Compared with more conventional methods of palliation such as laser therapy, patients with SEMS spent less time in the hospital and required less frequent reinterventions.\(^{163}\)


The main problems with SEMS are stent migration, tumor ingrowth or overgrowth, and, if placed across the GEJ, acid reflux. Placing uncovered stents across the cardia lessens the chance of migration, and stents have been developed with a 1-way flap valve to prevent reflux. It has also been shown that “tumor” ingrowth is sometimes due to granulation tissue or hyperplastic
reaction by the esophageal mucosa. Patency can be achieved again by laser, argon beam application, or sometimes placement of a second stent within the first. One recent randomized trial compared the use of the Ultraflex stent (Boston Scientific, Marlborough, MA) with the Polyflex stent (Boston Scientific), and the Niti-S double stent (Taewoong Medical, Seoul, Korea). The Polyflex stent is a silicone device with an encapsulated monofilament braid made of polyester. The silicone and polyester material are designed to lessen nontumoral tissue overgrowth, a problem common with SEMS. The Niti-S stent has an inner polyurethane layer over its entire length and an outer uncovered nitinol wire tube to allow the mesh to embed itself in the esophageal wall. Success rates were similar for all 3 stents, but recurrent dysphagia was more common with the Ultraflex stent because of tissue ingrowth and overgrowth and, to lesser degree, the Niti-S stent. Polyflex stent had a higher chance of migration, not surprisingly, because the stent is also designed to be removable in benign esophageal stenosis.

Another problem of stent insertion is placement near to the upper esophageal sphincter. Foreign body sensation, pain, odynophagia, and airway compression can be troublesome and demand accurate placement. This is illustrated in the situation when recurrent disease is found at the anastomosis or in the esophageal remnant after subtotal esophagectomy. Placement of SEMS is still possible and achieves good palliation.

SUMMARY AND FUTURE PERSPECTIVES

Significant improvement is evident in the management of esophageal cancer. Advancement of technology and proliferation of investigation and treatment modalities allow for precisely stratifying patients into various treatments. Surgeons play a key role in formulating therapeutic strategy for individual patients. More evidence-based staging systems and comprehensive staging modalities can help in patient selection. Data are evolving, and minimally invasive esophagectomy has been shown to be comparable, if not superior, to conventional approach for esophagectomy and has become standard surgical approach in many institutions. Neoadjuvant chemoradiotherapy integrated with surgery for locally advanced-stage disease seems better than either chemotherapy or radiotherapy alone, incorporated with surgery or as an adjuvant approach. Search for more effective and less toxic chemotherapeutic
agents and identification of predictors of chemoradiotherapy response should be the next direction of research in this area. The challenge for the future is for us to critically test our strategies in a scientific, unbiased manner and to explore other innovative treatments.

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Billroth and Czerny described the first esophageal resections in the 1870s, and these consisted of resections of the cervical esophagus without reconstruction. Later, resection of gastroesophageal (GE) junction tumors was performed by laparotomy with gastroesophageal anastomosis to reestablish intestinal continuity. Because there were concerns over respiratory compromise, surgeons were hesitant to enter the chest to perform esophageal resection. In 1915, Torek described the first transthoracic esophageal resection.\(^1\) He used a left thoracotomy to resect the esophagus but did not attempt reconstruction. Instead, a cervical esophagostomy and abdominal gastrostomy were performed. A 3-ft-long external rubber tube was used to connect the ostomies, and it allowed the patient to eat for 17 more years (Fig. 27-1). Turner performed the first transhiatal esophagectomy in 1933.\(^2\) Oshawa reported the first transthoracic resection of the esophagus with esophagogastric anastomosis in 1933.\(^3\) Knowledge of this procedure did not become widespread in the Western community until Adams and Phemister described the procedure in 1938.\(^4\)
FIGURE 27-1  A. Depiction of Torek’s first patient after esophageal resection. The rubber tube connected the lower end of the esophagus with a gastrostomy. The patient lived 17 years after the surgery and died at age 80.  
B. Removable rubber tube conduit with beveled ends. (Reproduced with permission from Torek F. The operative treatment of carcinoma of the oesophagus, *Ann Surg* 1915;April;61(4):385-405.)

Ivor Lewis is credited with popularizing transthoracic resection of the esophagus. Initially, he performed the procedure in two stages: first, mobilizing the stomach via laparotomy, and several days later resecting the intrathoracic esophagus and reconstructing with the stomach. The Ivor Lewis approach (which is an upper midline laparotomy for mobilization of the gastric conduit followed by right thoracotomy for resection and reconstruction) and the transhiatal approach are currently the two most commonly used techniques of esophageal resection. In 1962, McKeown described a tri-incisional approach. He used a right thoracotomy to mobilize the esophagus. The patient was then repositioned in the supine position, the gastric conduit was mobilized by laparotomy, and the anastomosis was performed in the neck. Minimally invasive options for surgical resection have also become increasingly popular. Thoracoscopic and laparoscopic techniques, robotic surgery, as well as combined minimally invasive with open approaches have created a wider variety of experiences and are
discussed in other chapters.

**NEOADJUVANT TREATMENT**

Historically, surgery has been the primary mode of treatment for localized esophageal cancer. Nonetheless, the long-term results of surgery alone for esophageal cancer are disappointing, with a 5-year survival of approximately 20%\(^8\)–\(^10\). Given the poor results with surgery alone, preoperative chemotherapy with or without radiation has been proposed as a means of improving long-term survival. Twelve randomized trials have been performed using preoperative chemoradiation, while nine additional randomized studies have evaluated the benefit of preoperative chemotherapy without radiation. Although two of the larger randomized trials comparing preoperative chemoradiation followed by surgery to surgery alone showed no difference in survival,\(^11\),\(^12\) several randomized trials have been used to support the use of preoperative chemoradiation.

Urba and colleagues looked at 100 total patients randomized to preoperative chemoradiation or surgery alone.\(^13\) Median survival was approximately 18 months in both groups; however, there was a trend toward improved survival at 3 years (30% vs 16%), albeit statistically insignificant.

Walsh and associates randomized 113 patients, and at 3 years there was a 32% survival benefit for those receiving preoperative cisplatin plus 5-FU and radiation (40 Gy) versus 6% for those undergoing surgery alone (\(p = 0.01\)).\(^14\) This study, however, has been heavily criticized for its lack of adequate pretreatment staging and survival in the surgical arm that is far below other reported series.

Cancer and Leukemia Group B 9781 (CALGB 9781) by Tepper and colleagues, evaluated patients with stage I to III esophageal cancer. Patients were randomized to surgery alone or to preoperative cisplatin and 5-FU with concurrent radiation (50.4 Gy) followed by surgery. Poor accrual resulted in premature closure of this underpowered study of 56 patients. Nonetheless, with median follow-up of 6 years, 5-year survival was 39% for the trimodality group versus 16% for the surgery-alone group (\(p = 0.002\)).\(^15\)

The 2012 Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) by Van Hagen et al. is a large multicenter study of 366 patients, and has been the most significant contribution supporting
neoadjuvant chemoradiotherapy. The chemoradiotherapy cohort was dosed carboplatin/paclitaxel with 41Gy of concurrent radiation prior to surgery. Findings were encouraging, with the achievement of an R0 resection in 92% of patients randomized to preoperative chemoradiation versus 69% in the group managed with surgery alone ($p < .001$). Five-year overall and disease-free survival were also significantly improved in the preoperative chemoradiotherapy group as compared to the surgery-alone cohort, with 47% and 34% overall survival. Median survival was 49 months in the neoadjuvant group versus 24 months in the surgery-only group. However, most of the benefit was seen in the squamous cell population. Survival in patients with squamous cell cancer had a hazard ratio of 0.422 ($p < .007$). Adenocarcinoma patient survival had a hazard ratio of 0.71 but with a $p$ value of 0.7, demonstrating a trend but not statistically significant difference.\textsuperscript{16}

In an effort to settle controversies arising from several conflicting study results, there are a number of meta-analyses comparing neoadjuvant chemotherapy or chemoradiotherapy to surgery alone. The most recent is by Sjoquist and associates, a 2011 update of the 2007 study by Gebski et al.\textsuperscript{17} The 2007 analysis reported a significant survival benefit for neoadjuvant chemoradiotherapy as well as neoadjuvant chemotherapy in patients with esophageal cancer. The update, with nearly 4000 patients, strengthened previous results, returning a hazard ratio of 0.78 (95% CI 0.70-0.88; $p < 0.0001$) corresponding to an absolute survival benefit at 2 years of 8.7% and a number-needed-to-treat of 11 with trimodality treatment.\textsuperscript{18}

A 2004 meta-analysis by Fiorica and colleagues included 734 patients, and returned similar findings with a significant improvement in 3-year survival with preoperative chemoradiotherapy versus surgery alone. However, this study also reported a significant increase in postoperative morbidity including respiratory complications, heart failure, and anastomotic leak in patients treated with neoadjuvant therapy.\textsuperscript{19}

Urschel and Vasan in 2003 combined the results of over 1100 patients from nine randomized controlled studies comparing neoadjuvant chemoradiotherapy followed by surgery versus surgery alone. This study also favored neoadjuvant chemoradiotherapy with surgery over surgery alone.\textsuperscript{20} These studies have led to the most recent (2015) National Comprehensive Cancer Network (NCCN) guidelines for the use of neoadjuvant chemoradiation in medically and surgically fit patients diagnosed with
resectable, locally advanced esophageal cancer of the GE junction.21

Similar to the studies evaluating the potential survival gain with preoperative chemoradiotherapy, there is substantial comparative evidence of the benefit of neoadjuvant chemotherapy without radiation for locally advanced esophageal cancer. The largest of such studies is the Medical Research Council (MRC) esophageal cancer (OEO2) trial of 2002, which was updated in 2009.22,23 Both the original and long-term studies demonstrated a statistically significant survival benefit (23% vs 17%) and progression-free survival in those patients who received preoperative chemotherapy. A comparable well-sized US study by Kelsen et al. was published in 1998. The original results of this study, however, were contradictory, displaying no evidence of a difference in the disease-free or overall survival between the two treatments.24 Nonetheless, a 2009 update of this trial did report the necessity for complete resection with negative microscopic margins, as only patients who underwent an R0 resection had a substantial chance of long-term disease-free survival.25

These reports were followed by the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial in 2006. This study looked at GE junction tumors including those that were considered gastric, an important group that had been excluded from many earlier studies. This trial demonstrated an improved survival at 5 years of 36% versus 23% in patients with GE junction adenocarcinoma treated with preoperative chemotherapy.26

Although many of these studies suggest that neoadjuvant treatment may prove beneficial, there still remains controversy about the use of chemotherapy versus chemoradiotherapy. Two head-to-head comparisons of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy have been completed to date. Both studies, however, were underpowered and consequently unable to determine a statistically significant survival advantage. The first trial by the German Esophageal Cancer Study Group did display a trend toward improved survival with trimodality therapy.27 The second study by Bermeister and colleagues did not share this trend.28 Unfortunately, no clear determination has been made regarding which method is better. The relatively low incidence of esophageal cancer, the variable response to treatment between squamous cell carcinoma and adenocarcinoma, and the regional practice patterns make a large, randomized study difficult to envision.
STAGING

It is important to recognize those patients with stage IV disease, because the mean survival in these patients is 6 to 10 months. In the past, palliative esophagectomy was thought necessary to restore swallowing and oral nutrition. With advances in photodynamic therapy, expandable endoscopic stents, and other endoluminal therapies, it is unusual for anyone to require esophageal replacement to reestablish swallowing ability. Hence, stage IV patients should be spared the perioperative mortality, morbidity, and recovery time associated with esophagectomy. The appropriate use of neoadjuvant treatment requires accurate staging. Patients with nodal involvement, invasion through the esophagus, or possibly even invasion into the muscularis often undergo preoperative chemoradiation, while patients with simple mucosal involvement generally proceed directly to endoscopic treatment or surgical resection.

The main staging modalities available today are computed tomography (CT) scan, positron emission tomography (PET) scan, and endoscopic ultrasound (EUS). CT scans are used mainly for detecting distant metastases in the lungs, liver, or other remote sites, including the brain. CT scan may be useful for excluding T4 tumors if a fat plane can be demonstrated between the adjacent structure and the esophagus. Such staging is often not possible if the patient is severely cachectic or if there are no natural fat planes, such as that between the trachea and esophagus. In regard to nodal status, CT is not as sensitive or as accurate as EUS.

PET scan is superior to CT scan for detecting distant metastatic disease. In a series of 91 patients, CT scan had a sensitivity of 46%, a specificity of 74%, and an overall accuracy of 73%. In contrast, PET scan had a sensitivity of 69%, specificity of 93%, and overall accuracy of 84%. All metastases that were missed by PET were less than 1 cm in size. Other studies have shown similar results. In addition, PET scan may aid in the diagnosis of primary tumor where it may be difficult to perform biopsy because of obstruction. Conversely, a certain percentage of nonbulky tumors of the esophagus may be PET-negative.

EUS gives detailed images of the esophageal wall and nearby structures (Fig. 27-2). Accurate identification of the layers of the esophageal wall is possible. Muscle layers tend to be hypoechoic with intervening hyperechoic mucosal layers. The first and second hypoechoic layers correspond to the
mucosa and muscularis mucosa, respectively. The third hyperechoic layer is submucosa. The fourth hypoechoic layer is the muscularis propria, and the fifth hyperechoic layer is the outside of the esophagus. Tumor infiltration of the wall disrupts the normal-layered appearance, and extent of penetration is usually clearly visible. EUS has an overall accuracy of 80% to 90% in ascertaining T status. The differentiation between T1 and T2 is most difficult. In addition, biopsy of deeper layers of tumor not accessible by traditional grasping forceps is possible. It should be noted that EUS is not accurate in defining postneoadjuvant treatment T status because of fibrosis induced by the chemoradiation.

**FIGURE 27-2** Endoesophageal ultrasound image of an adenocarcinoma of the esophagus (T3) and multiple lymph nodes suspicious for metastatic disease (N1). (Reproduced with permission from Van Dam J, Sivak MV, Catalano MF et al: High-grade malignant stricture is predictive of esophageal tumor stage: risks of endosonographic evaluation, *Cancer* 1993;May 15:71(10):2910-2917.)
Nodal status is determined by examining four characteristics. Malignant nodes tend to be round and hypoechoic. They have discrete borders and are larger than 1 cm in size. Nodes that meet such criteria have a 90% chance of being malignant. Fine-needle aspiration (FNA) further increases the accuracy in determining nodal status. If the tumor is from a node, the cytopathologist should be able to identify lymphoid tissue in the specimen. False positives can result with FNA if the needle passes through the primary tumor. The accuracy of EUS in N-status staging is between 70% and 80%. EUS is 10% to 15% more accurate than CT scan.\textsuperscript{31}

Developments in EUS and PET scanning have lessened the enthusiasm for preresection operative staging of esophageal cancer patients. Operative staging involving laparoscopy and thoracoscopy is more invasive but may be superior to EUS. Luketich and associates studied 26 patients and detected N1 disease in a considerable number of patients staged N0 by EUS.\textsuperscript{32} It should be noted, however, that the sensitivity of EUS in this series was only 60%, considerably lower than that described in other series. In addition, 15% of patients with no radiographic metastatic disease were found to have liver metastases by laparoscopic staging. The average cost of surgical staging was $20,000 to $25,000 versus $2000 for EUS.

A common algorithm used in staging patients includes endoscopy for primary diagnosis, CT scanning with PET to evaluate for metastatic disease, and EUS if the patient is an operative candidate and neoadjuvant therapy is considered. In cases of esophageal obstruction, where EUS scanning is known to be less accurate, the incidence of lymph node metastasis is very high (90%), and neoadjuvant therapy should be considered.

**APPROACH TO THE CERVICAL LESION**

The treatment of a cancer of the cervical esophagus is challenging and requires a multidisciplinary approach involving an otorhinolaryngologist, a thoracic surgeon, and occasionally a plastic surgeon. Frequently, radiation will be required preoperatively to maximize margins and spare the larynx, if possible. The neck incision is made along the anterior border of the sternocleidomastoid muscle and can be extended across the midline if additional exposure is needed. If the tumor is fixed to the spine or neck vessels, the procedure is aborted and palliative radiotherapy is considered. If
the larynx is involved, it is removed en bloc with the upper esophagus along with the upper paraesophageal nodes bilaterally. A radical neck dissection is not routinely performed. The dissection spares the jugular vein, sternocleidomastoid muscles, and spinal accessory nerves. The trachea is transected, leaving enough length to allow construction of a permanent end tracheostomy. The endotracheal tube is inserted into the distal trachea and the hypopharynx is divided sharply.

By this point, a separate midline abdominal incision will have been performed, and blunt dissection is begun on the esophagus from the abdomen. A two-team approach should be considered, with one team at the neck while the other prepares the gastric conduit. The gastric conduit is elevated to the neck with traction and the gastroesophageal junction is divided. The pharyngogastrostomy anastomosis is performed using a single-layer, interrupted hand-sewn anastomosis with a nonabsorbable suture. The cervical tracheostomy is performed above the sternal notch. If too much trachea has been resected to allow for this, manubrial resection will permit placement of the end tracheostomy lower in the midline.

**STRATEGY FOR LESIONS BELOW THE THORACIC INLET**

Lesions below the thoracic inlet can be divided according to their location in the upper esophagus (below the thoracic inlet but above the carina), midesophagus (between the carina and inferior pulmonary vein), or lower esophagus (below the inferior pulmonary vein). While we favor the tri-incisional approach for all malignant lesions (for reasons discussed later), lesions in the upper thoracic esophagus generally must be approached with this technique to ensure adequate proximal margins. If the lesion is in the midthoracic esophagus, either the tri-incisional approach or the Ivor Lewis approach may be adequate. Lower esophageal tumors can be resected with either of these two approaches, or additionally with a transhiatal approach, or left thoracotomy and distal esophagectomy. With any resection, accommodation must be made for additional resection with reconstruction if frozen margins are involved with tumor.
Transhiatal versus Transthoracic Techniques

Five prospective, randomized trials have been performed comparing transhiatal to transthoracic resection. The first was published in 1993 by Goldmine and associates. Sixty-seven patients younger than 70 years with squamous cell cancer were randomized to Ivor Lewis resection or transhiatal resection. Operative time was longer (6 vs 4 hours) in the Ivor Lewis group. There was no difference in the incidence of pneumonia (20%), anastomotic leak, recurrent nerve injury, bleeding, perioperative mortality, or length of hospital stay. For those patients with nodal disease, however, none of the transhiatal patients were alive at 18 months, while 30% of the transthoracic patients were alive at 18 months.

The most recent randomized trial is from 2006. This study from Pakistan by Areja and associates found no significant difference between the two approaches. However, this study, like many before it, was limited, with only 30 patients.

Chu and coworkers randomized 39 patients with lower-third esophageal cancers to either Ivor Lewis or transhiatal resection. Limitations of the study were small sample size, short follow-up (mean 15 months), and patient exclusions. Patients undergoing neoadjuvant therapy or those with forced expiratory volume in 1 second (FEV) less than 70% of expected were excluded. There were no perioperative deaths in either group. Intraoperative hypotension occurred in 60% of transhiatal patients but only in 5% of transthoracic patients. There was no difference in blood loss, pneumonia, or recurrent nerve injury. The mean proximal margin was 3 cm longer in the transhiatal group. No significant difference was seen in tumor recurrence or survival during the brief follow-up period.

A study comparing transhiatal resection to transthoracic, tri-incisional en bloc resection for distal adenocarcinoma of the esophagus or cardia was performed in the Netherlands. One hundred and six patients were randomized to transhiatal resection and 114 patients to transthoracic resection. In-hospital mortality was 2% to 4% in each group. Chyle leak was higher in the transthoracic resection group (10% vs 2%). Respiratory complications including atelectasis and pneumonia were higher in the transthoracic group (57% vs 27%). Although statistical significance was not reached, 39% of the transthoracic group was alive at 5 years, while only 29% of the transhiatal
An update of this study following with a full 5-year follow-up continued to show no statistically significant overall survival in either approach. However, in a subgroup of patients who had one to eight positive lymph nodes in the resection specimen, the transthoracic approach (TTE) demonstrated improved overall survival compared with the transhiatal approach (THE) (39% TTE vs 19% THE, \( p = 0.05 \)). Disease-free survival was similarly improved with the transthoracic approach (64% TTE vs 23% THE, \( p = 0.02 \)).

Thirty-two patients were included in a trial by Jacobi et al. This trial sought to determine if there was a difference in perioperative pulmonary function between the two approaches by measuring several cardiopulmonary parameters. They found a significant increase in operative time, blood loss, and need for transfusion in the transthoracic approach. Although there was a slight increase in intraoperative pulmonary strain during single-lung ventilation in the transthoracic patients, this was well compensated and transient. Additionally, the pulmonary disturbance did not correlate to a significant difference in postoperative cardiopulmonary events, 30-day mortality, anastomotic leak, or 1-year survival (70% THE vs 77% TTE). Of note, the patients in this study were highly selected and included in the study only if they were aged less than 75 years and free of cardiac, pulmonary, or renal dyscrasia.

The randomized trials show no statistically significant difference in survival, but they are small, and trends toward improved survival are observed in patients undergoing transthoracic dissection. No difference in mortality have been detected in the completed trials thus far.

The analyses summarized above have been performed in an attempt to quell the debate of the superiority of either transhiatal or transthoracic approach. Three meta-analyses to date have attempted to determine the most appropriate approach to the surgical treatment of esophageal cancer. Boshier and colleagues reviewed 52 English-language studies between 1981 and 2009. Comparable to other meta-analyses, there was no significant difference in 5-year survival, postoperative cardiac complications, hemorrhage, acute respiratory distress syndrome/acute lung injury, chyle leak, and renal insufficiency. Significant differences were found with the extent of lymphadenopathy, with a mean resection yield of eight more lymph nodes found with the TTE. Additionally, the TTE was found to have an
increased incidence of pneumonia (21% vs 17%), early (<30 days or in hospital), mortality (10% vs 7%), and a prolonged length of stay of 4 days as compared to the THE. The THE, however, was found to have a statistically significant increase in anastomotic leak (17% vs 10%), anastomotic stricture (25% vs 21%), and vocal cord paralysis (11% vs 5%). A subgroup analysis of 22 studies published after 1999 was also completed. Surprisingly, this analysis of more recent studies determined that the differences in anastomotic leak, vocal cord paralysis, and pneumonia were no longer significant.

Rindani and associates reviewed 44 trials involving either Ivor Lewis or transhiatal esophagectomy that were published in the English language between 1986 and 1996. Overall, the incidence of bleeding, cardiac complications, or pneumonia was no different between the two groups. Differences were seen in the anastomotic leak rate (16% transhiatal vs 10% Ivor Lewis), stricture rate (28% transhiatal vs 16% Ivor Lewis), and incidence of recurrent nerve injury (11% transhiatal vs 5% Ivor Lewis). Mortality was higher after the Ivor Lewis approach (9.5%) than the THE (6.3%). Long-term survival was approximately 25% with either technique.

Hulscher and colleagues performed a meta-analysis of 50 studies published between 1990 and 1999 involving transthoracic and transhiatal resection. Cardiac complications (20% vs 7%), anastomotic leakage (24% vs 7%), and vocal cord paralysis (10% vs 4%) were higher in the transhiatal group as opposed to the transthoracic group. Pulmonary complications (19% vs 13%), in-hospital mortality (9% vs 6%), and operative time (5 vs 4.2 hours) were higher in the transthoracic group. Overall long-term survival was similar between the two groups (23% for transthoracic and 21.7% for transhiatal resections).

It is important to note that these meta-analyses are retrospective and nonrandomized. In addition, reported surgical quality was suboptimal in both approaches, and the transthoracic group was noted to have more advanced cancer. Caution should therefore be used in applying these findings to individual institutions and patients.

Several patient factors must be considered when choosing the operative approach to esophageal resection. Some argue that transhiatal dissection may be less taxing on an elderly or debilitated patient (due to shorter operative time or avoidance of a thoracotomy). Many surgeons experience hemodynamic changes with transhiatal resection presumably due to compression during blunt dissection. Wong reported intraoperative
hypotension in 60% of transhiatal dissections, but in only 5% of transthoracic dissections, suggesting that the transhiatal operation may be more taxing to a patient with severe cardiac valvular or atherosclerotic disease who cannot tolerate fluctuations in blood pressure. This finding, however, was not corroborated by the Jacobi study.

**SURGICAL APPROACHES TO LESIONS BELOW THE THORACIC INLET**

**Tri-Incisional Esophagectomy (McKeown Technique)**

The tri-incisional technique of esophageal resection combines the most attractive aspects of the Ivor Lewis and transhiatal approaches. It allows for dissection of the intrathoracic esophagus under direct vision with complete nodal resection and brings the anastomosis to the neck, allowing for maximal proximal margins and minimizing the risk of an intrathoracic leak.

Under general anesthesia, bronchoscopy is performed to rule out tracheal or bronchial (most commonly left main bronchial) involvement with tumor. Esophagogastroduodenoscopy is performed to localize the tumor and rule out disease of the stomach or duodenum. The patient is then reintubated with a double-lumen endotracheal tube and placed in the left lateral decubitus position. A right posterolateral thoracotomy incision is made large enough, approximately 10 cm in length, to introduce the surgeon’s hand (Fig. 27-3). The serratus muscle is spared. Division of the intercostal muscles anteriorly and posteriorly often permits adequate rib spreading without the need to remove a small portion, or shingle, of rib. The chest is entered through the fifth or sixth interspace, depending on the location of the tumor. The inferior pulmonary ligament is divided using electrocautery, and the lung is retracted anteriorly.
FIGURE 27-3  A. The right chest has been entered through the fifth interspace. A piece of the posterior sixth rib has been “shingled” to aid in exposure. The lung is retracted anteromedially, and the mediastinal pleura has
been incised posteriorly to expose the esophageal tumor. *Inset:* The patient is placed in the left lateral decubitus position. The *dotted line* marks the skin incision for a right posterolateral thoracotomy. **B.** The latissimus muscle is divided as caudally as possible, and the serratus muscle is spared and reflected medially.

Dissection of the esophagus begins at a point away from tumor and any associated scarring, and the esophagus is encircled with a Penrose drain. Traction on the Penrose drain allows for cautery dissection encompassing all adjacent nodes. Arterial branches directly off the aorta are clipped or ligated. The settings on the electrocautery should be low when cauterizing near the trachea. The azygos vein is typically divided, although this is not always necessary (*Fig. 27-4*). At this level, the vagus nerves are identified. Dissection cranial to this level involves the vagus nerves; the vagus nerves are peeled off and away from the esophagus to avoid injury to the recurrent vagus branches.
FIGURE 27-4  The esophagus has been isolated circumferentially at a point superior to the tumor and encircled with a Penrose drain. An endostapling device is used to divide the azygos vein near its caval connection.

Dissection between the trachea and esophagus must be done with care and with low cautery dissection to avoid injury to the membranous trachea. Much of the dissection high in the chest can be done bluntly (Fig. 27-5). The cranial aspect of the dissection is complete when one’s fingers reach easily above the first rib. The Penrose drain is knotted and passed into the lower neck with the knot against the vertebral body for later retrieval during the neck phase of the dissection (Fig. 27-6).
FIGURE 27-5  With countertraction applied to the Penrose drain encircling the esophagus above the tumor, blunt finger dissection is used to develop the tracheoesophageal plane to and above the thoracic inlet.
The knotted Penrose drain is pushed up through the thoracic inlet and left to lie beneath the omohyoid muscle on the left side of the neck.

Another Penrose drain is used to gain traction on the lower esophagus, and dissection continues caudally. All tissue between the pericardium, aorta, and azygos vein is dissected and incorporated into the specimen. No effort is made to resect the thoracic duct, although it is sometimes injured. For tumors near the gastroesophageal junction, a rim of diaphragm is incorporated into the specimen. The knotted Penrose drain is placed in the abdomen for later retrieval (Fig. 27-7). At this point, careful inspection is made for hemostasis and injury to the thoracic duct. Often, injury to the thoracic duct is evident when slightly cloudy or crystallized fluid is seen pooling in the region of the duct. If an injury to the duct is seen, it should be closed with a pledgeted fine suture such as 5-0 Prolene. Mass ligature of the duct, as it enters the chest, is then performed by encompassing all tissue between the spine, aorta, and azygos vein at the level of the hiatus with a 0-silk suture. A 28-Fr straight
A chest tube is inserted via a separate stab incision and directed to the apex of the chest. An additional hole in the tube can be made to facilitate dependent fluid drainage. The ribs are reapproximated with 2-0 Vicryl sutures. The latissimus layer is closed using a running 0 Vicryl suture. A subdermal layer is closed with 2-0 Vicryl and the skin is closed in subcuticular fashion.

**FIGURE 27-7** The lower Penrose drain is pushed down onto the gastroesophageal junction below the diaphragm. The thoracic duct is shown ligated, and a rim of the diaphragmatic hiatus encircles the lower esophagus.

The patient is placed in the supine position and is reintubated with a single-lumen tube. A roll is placed under the back to permit neck extension, and the head is turned to the right. A midline laparotomy is performed from the umbilicus to the xiphoid. Exploration of the abdomen should include a careful palpation of the liver and inspection of the serosal surfaces for tumor implants. Palpation of the GE junction and proximal stomach should be
performed to rule out gastric spread of tumor. The left lobe of the liver is mobilized and retracted to the right. The Penrose drain left from the chest dissection is used for retraction of the GE junction (Fig. 27-8). The gastroepiploic artery is identified and palpated. The pulse should be easily palpable provided the patient has a physiologic blood pressure. Staying at least 2 cm away from the gastroepiploic artery, the lesser sac is entered. Dissection continues cranially on the stomach along the greater curvature. Dissection may be performed by dividing tissue and ligating with 2-0 silk ties or by using an ultrasonic scalpel. The stomach is retracted medially and the omentum laterally. The artery itself should not be grasped or used for retraction. The gastroepiploic arcade ends near the point where the short gastric arteries begin. A pack placed behind the spleen often aids in exposure of the short gastric vessels (Fig. 27-9). The short gastric vessels can be ligated, double-clipped, or divided with an ultrasonic scalpel. Large vessels should be tied. Care should be taken not to incorporate stomach wall in the ligature, as this may result in delayed necrosis of stomach wall and a postoperative intrathoracic leak. Dissection on the greater curvature proceeds to the hiatus and is complete when the Penrose drain is reached.

**FIGURE 27-8** Exposure achieved by upper midline laparotomy. The large Balfour retractor is on the lateral abdominal walls, and the upper hand
retractor reflects the liver to the right, exposing the hiatus and lower Penrose drain around the GE junction.

**FIGURE 27-9** Gastric mobilization is begun at the superior greater curvature near the hiatus. A rolled Mikulicz pad is placed behind the spleen to aid in exposure. The short gastric vessels between the spleen and the stomach are divided, and the transition zone between the left and right gastroepiploic arteries is identified. Mobilization proceeds at least 2 cm away from the right gastroepiploic arcade (dotted line).

Proximal dissection on the greater curvature of the stomach proceeds in likewise fashion. The gastroepiploic artery migrates farther from the stomach as one dissects toward the pylorus, and care must be taken not to injure the vessel. The gastrohepatic ligament is divided with cautery up to the GE junction. The stomach is lifted anteriorly, and thin adhesions between the
stomach and pancreas are divided with cautery. The left gastric vessels are approached from behind the stomach (Fig. 27-10). The vessels are skeletonized, and lymph nodes are swept up onto the specimen. The vessels are clamped with a vascular endoscopic 30-mm stapler. The gastroepiploic pulse should be palpated at this time to ensure that the celiac axis itself has not been clamped, and the stapler is then fired. The duodenum is then mobilized using a Kocher maneuver, bringing it to the midline (Fig. 27-11). A pyloromyotomy or pyloroplasty may be performed with equivalent efficacy in aiding gastric emptying. If a pyloroplasty is performed, it is best to close it in a single layer with interrupted (3-0 silk) sutures. A leak is exceedingly rare.

**FIGURE 27-10** After the greater curvature is mobilized, the stomach is reflected superiorly and to the right, exposing the left gastric artery and coronary vein. These are ligated and divided with an endostapler, near their origin, from the celiac axis.
A neck incision is then made 6 cm in length along the anterior border of the left sternocleidomastoid muscle starting at the sternal notch. Deep to the platysma, dissection proceeds medial to the sternocleidomastoid muscle and carotid sheath and lateral to the thyroid. The omohyoid can be divided with cautery (Fig. 27-12). Blunt dissection is then used to approach the vertebral bodies (Fig. 27-13). Lying along the vertebral body, the Penrose drain is grasped and brought out into the neck wound with the encircled esophagus. Proximally, the esophagus can be gently mobilized. The nasogastric tube is removed, and the esophagus is divided with a GIA 75-mm stapler (Fig. 27-14). A 2-silk suture is attached to the proximal margin, and the specimen is drawn out into the abdomen (Fig. 27-15). The cervical end of this tie is fastened to a clamp.
FIGURE 27-12  Anatomic structures of the left neck below platysma level. The incision line along the medial border of the sternocleidomastoid muscle is shown. Division of the omohyoid muscle along with ligation of the middle thyroid vein allows for exposure of the underlying esophagus.
FIGURE 27-13  Left cervical incision with the sternocleidomastoid muscle reflected laterally. Finger dissection beneath the omohyoid muscle develops a plane to the knotted Penrose drain. The patient is placed supine for the neck and abdominal incisions (*inset*).
FIGURE 27-14 A GIA stapler is used to divide the cervical esophagus. Note the ligated middle thyroid vein and divided omohyoid muscle. Inset: Traction is placed on the Penrose drain around the cervical esophagus.
FIGURE 27-15 The specimen is removed through the abdominal incision with a long heavy silk suture attached to the end of the esophagus.

The gastric tube is then constructed by resecting the GE junction and the lesser curvature of the stomach down to the crow’s foot of veins with a series of thick tissue 75-mm gastrointestinal anastomosis (GIA) staplers (Fig. 27-16). A narrow gastric tube is believed to aid in emptying; however, a diameter of less than 5 to 6 cm may compromise conduit perfusion. The right gastric artery along the lesser curvature can be divided in order to allow elongation of the conduit (Fig. 27-17). The specimen is removed, and frozen
sections are performed on the margins. Inspection for hemostasis is made of the gastric bed. The esophageal hiatus should admit four fingers. One ampule of IV glucagons is administered to ensure relaxation and lengthening of the gastric conduit. The silk tie that traverses the mediastinum is then attached to the valved end of a Foley catheter with a 30-cc balloon (Fig. 27-18). An endoscopic camera bag is secured around the 30-cc balloon (Fig. 27-19). The conduit is advanced into the bag, ensuring appropriate orientation. Suction is applied to the bag via the Foley catheter, and the conduit is drawn up into the neck incision (Fig. 27-20). The assistant must actively guide the conduit through the hiatus. At the end, the pylorus should sit at the hiatus.

**FIGURE 27-16** The stomach is mobilized as a pedicle based on the right gastroepiploic vessels. *Inset: Incisions illustrated.*
FIGURE 27-17  The right gastric artery and lesser omentum are divided with an endostapling device. *Inset:* A GIA stapler divides the stomach along the lesser curvature, creating the gastric conduit.
FIGURE 27-18 The heavy silk is tied to the port of a 30-cc balloon Foley catheter and is pulled up partially through the neck incision.
FIGURE 27-19  An arthroscopy camera bag is tied around the Foley catheter balloon and the gastric conduit is placed in the folded-up arthroscopy bag ensuring the proper axial orientation. *Inset:* A Yankauer suction is attached to the Foley catheter to collapse the bag around the neoesophagus.
FIGURE 27-20 The gastric conduit is atraumatically pulled through the posterior mediastinum into the cervical wound.

The neck anastomosis can be hand-sewn using interrupted full-thickness 3-0 silk sutures (Fig. 27-21). The anastomosis may also be stapled in side-to-side, functional end-to-end fashion. A portion of the esophageal staple line is removed, an enterotomy is created on the posterior aspect of the gastric tube, and a linear GIA 75-mm stapler is inserted to create the anastomosis (Fig. 27-22). An additional fire of an endoscopic 30-mm stapler may be used to gain additional length on the anastomosis. The enterotomy is usually closed with a TA 30 or 60 stapler after guiding the nasogastric tube down toward the
hiatus. Hybrid anastomosis has been described with the back wall of the anastomosis created using a 30-mm stapler and the anterior wall closed with sutures. A soft drain should be placed posterior to the anastomosis, and the platysma and skin are closed separately. It is wise to use an interrupted closure, as this will allow for reopening of a portion of the wound should a cervical leak develop. Before closing the abdomen, a J-tube should be inserted at a point approximately 40 cm distal to the ligament of Treitz. The fascia is closed using a #2 running monofilament suture and the skin is closed with staples.

**FIGURE 27-21** The esophagogastric anastomosis is performed with a single layer of full-thickness interrupted nonabsorbable sutures. The Silastic sump drain is shown emanating from the fundus of the gastric conduit. A Jackson-Pratt drain is shown positioned alongside the gastric conduit inferiorly and exiting from a separate stab wound above the clavicle.
FIGURE 27-22  A. and B. The stapled functional end-to-end anastomosis is performed using the GIA stapler to approximate the side of the esophagus to the anterior wall of the stomach. C. The TA linear stapler is then used to close the defect between the two free walls.

Ivor Lewis Technique

The patient is placed in the supine position. Bronchoscopy to rule out tracheobronchial invasion and esophagoscopy to confirm the location of the tumor are performed. An upper midline incision is made from the umbilicus to the xiphoid. The abdominal phase of this operation is identical to the previously described tri-incisional technique. Enlargement of the hiatus and dissection of the lower esophagus are more easily performed through the abdomen than through a high thoracotomy incision. The GE junction and
lesser curvature of the stomach are resected using a GIA stapler. The specimen is left attached to the esophagus to facilitate mobilization into the chest. A J-tube is placed before closing the abdomen.

A double-lumen endotracheal tube is placed and the patient is repositioned in the left lateral decubitus position. A right posterolateral thoracotomy is performed, and the chest is entered through the fourth or fifth interspace. The azygos vein is divided and the intrathoracic esophagus is dissected. All lymphatic tissue is included with the esophagus. Because a gross margin of 5 cm, and ideally 10 cm, is desired, the anastomosis is usually performed high in the chest at or above the level of the azygos vein. The proximal esophagus is dissected only several centimeters above the proposed level of transection to preserve its blood supply. The mobilized stomach is pulled up into the chest. The anastomosis can be constructed using an EEA stapler or hand-sewn technique. If a hand-sewn anastomosis is chosen, a double-layer technique is advisable. In 1942, Churchill and Sweet described a method of double-layer anastomosis that is still often used today. A point on the gastric tube at least 2 cm away from the staple line is chosen for the anastomosis. A circle of stomach serosa 2 cm in diameter is scored and the underlying gastric vessels are ligated with 4-0 silk sutures. The back outer layer of the anastomosis is constructed with interrupted 4-0 silk horizontal mattress sutures. These are placed 4 mm away from the serosal edge. Full-thickness stomach and esophageal wall are used. The esophagus is opened with a sharp instrument and the inner layer is constructed with interrupted suture incorporating esophageal mucosa and full-thickness stomach edge. The nasogastric tube is passed after completion of the posterior wall. A continuous Connell suture may also be used. The anterior outer layer anastomosis is constructed with 4-0 silk horizontal mattress sutures. The anastomosis should be wrapped or buttressed with omentum. At all times, atraumatic handling of mucosal edges and tying of sutures without crushing of tissues are advised. Some surgeons advise tacking the edge of the stomach wall to mediastinal tissue or paravertebral fascia to decrease tension on the anastomosis, although it is not clear if this is necessary. A 28-Fr straight chest tube is placed into the apex of the chest via a separate stab incision. The chest is closed with interrupted #2 Vicryl paracostal sutures, followed by a 0 Vicryl running latissimus layer, a 2-0 Vicryl running subdermal layer, and a 3-0 Vicryl subcuticular layer. Postoperative toilet bronchoscopy should be performed.
Transhiatal Technique

CONSIDERATIONS

We believe that a tri-incisional approach gives better exposure to the thoracic esophagus, allowing for a safer and wider resection and better lymphadenectomy. As discussed, there may be survival advantages to the radical resection permitted by the transthoracic technique, although trials to date have not shown a statistically significant survival advantage using this approach. In cases in which the thoracic esophagus is not involved with tumor (either high-grade dysplasia or a laryngeal tumor involving the proximal esophagus), the transhiatal technique may be performed with equivalent oncological efficacy.

TECHNIQUE

The patient is placed in the supine position with the head rotated 45 degrees to the right. The abdominal phase of the operation is performed in identical fashion to that described in the tri-incisional section above. An upper-hand retractor is useful in elevating the sternum and costal margin. The
phrenoesophageal ligament is divided using cautery, and the lower esophagus is encircled with a 1-in wide Penrose drain. The phrenic vein must first be identified and ligated. This will also enlarge the window for dissection of the intrathoracic esophagus. The hiatus is dilated to allow entry of the surgeon’s hand. Arterial branches from the aorta are clipped on the aortic side and divided using cautery. Thin handheld malleable retractors are used to retract either side of the pleura during the dissection. Dissection under direct vision is usually possible up to the level of the inferior pulmonary veins.

At this point, an incision is made in the left neck along the anterior border of the sternocleidomastoid muscle starting at the sternal notch and extending 6 to 8 cm. The platysma is divided. The sternocleidomastoid muscle and carotid sheath are retracted laterally. The omohyoid is often divided. The middle thyroid vein is ligated and divided. A retractor may be used but must not rest on the recurrent nerve in the tracheoesophageal groove. The esophagus is palpated anterior to the spine and posterior to the trachea. Sharp dissection is carried out immediately on the esophagus, separating the esophagus from the membranous trachea and recurrent nerve. The esophagus is looped with a 1-in Penrose drain.

Blunt dissection of the posterior plane of the esophagus is performed first. From the abdomen, the surgeon’s hand is placed in between the spine and esophagus with the palmar aspect of the fingertips immediately against the esophagus (Fig. 27-24). This is performed in conjunction with raising the esophagus anteriorly with the aid of the Penrose drain. An identical maneuver is performed through the cervical incision. When sufficient dissection has been done from either side, both hands are introduced simultaneously and an attempt is made to touch fingertips. Intervening loose areolar tissue must then be torn, uniting the fingertips. If the surgeon’s fingertips will not reach from the neck, a sponge stick can be used. While the surgeon’s hand is behind the heart, there must be constant communication between the surgeon and the anesthesiologist. Hypotension often results from compression of the left atrium and impairment of left ventricular filling. It is wise to have the arterial line tracing and numbers in direct view of the surgeon; the surgeon’s eyes should be on these numbers as he/she performs the blind dissection with his/her fingers.
Dissection anterior to the esophagus is then performed in nearly identical fashion. The palmar aspect of the hand is again kept directly against the esophagus (Fig. 27-25). As dissection approaches the carina from below, the surgeon will note an increase in the tenacity of the anterior attachments to the esophagus. Dissection must be gentler in this area. A gentle side-to-side motion of the fingertips will also separate the trachea from esophagus. Eventually the fingertips from both hands are united. Once the anterior and posterior dissection has been completed, the lateral attachments are then divided. From the neck incision, as much blunt dissection of the lateral attachments as possible is performed under direct vision. Next the surgeon’s hand is introduced anterior to the esophagus with the palmar aspect of the hand facing the esophagus. The hand is inserted until the first and second fingers are above the level of dissection of the lateral attachments. These attachments are pressed against the spine, and using a raking motion the surgeon pulls his hand back toward the abdomen, releasing the lateral attachments (Fig. 27-26). Care must be taken in the region of the azygos vein and its branches.
FIGURE 27-25  Anterior blunt dissection of the esophagus in the chest. Dissection must be gentle and deliberate around the level of the carina to avoid tracheal as well as azygos vein injury.

FIGURE 27-26  The esophagus has been freed from the trachea, and the lateral attachments are avulsed from a cranial to caudal direction.

The remainder of the operation, including the anastomosis, is identical to that of the tri-incisional technique. After removing the specimen, it is wise to pack the mediastinum with a lap pad (without compressing the heart) to facilitate hemostasis. Prior to drawing the conduit into the neck, a final inspection is made for hemostasis and for entry into either pleural space. If either pleural space is entered, a chest tube should be placed.
Left Thoracoabdominal Approach

CONSIDERATIONS

Limited resection of the distal esophagus via left thoracotomy is almost always a compromise procedure. Only the distal esophagus is readily accessible via the left chest, as the aortic arch obscures much of the upper esophagus. A tumor that extends more proximally than 30 cm should not be approached through the left, as a difficult dissection behind the aortic arch will be required. In addition, placement of the esophagogastric anastomosis low in the left chest can be associated with severe GE reflux. This approach is best reserved for a GE junction cancer that involves a significant portion of the proximal stomach and when there is concern that the residual stomach may be of insufficient length to reach the neck.

A variety of incisions or a combination of left thoracic and abdominal incisions can be used for this approach. An upper midline laparotomy can be extended across the costal margin. This is the least versatile approach and its use is limited to instances in which use of the esophagus is unexpected, as with proximal extension of a gastric tumor. A second approach involves placing the patient in full right lateral decubitus position and taking the diaphragm down in radial fashion 2 to 3 cm from the chest wall to gain exposure to the abdomen. This approach permits good exposure to the upper abdomen, although exposure to the pylorus and duodenum may be difficult.

TECHNIQUE

The most versatile thoracoabdominal approach involves positioning the patient in the right lateral decubitus position with the hips rotated posteriorly 45 degrees. A left sixth interspace thoracotomy is performed beginning at the tip of the scapula and extending across the costal margin toward the abdominal midline. The costal margin is divided with a rib cutter. The left lung is deflated. The diaphragm is incised circumferentially 2 to 3 cm away from the chest wall (Fig. 27-27). Doing so avoids injury to the radial branches of the phrenic nerve. A novel technique is to use the endo GIA staplers along the periphery of the diaphragm. This provides some structure to sew to when reconstructing the diaphragm. The abdomen is explored for metastatic disease. Cautery is used to divide the inferior pulmonary ligament.
The mediastinal pleura overlying the esophagus is incised, and the esophagus is encircled in the lower chest including all tissue from the aorta to the pericardium. The esophagus is dissected proximally behind the inferior pulmonary vein. A proximal gross in situ margin of 10 cm is ideal, though lesser margins, if confirmed negative by frozen section, may be adequate. A point of division of the proximal esophagus is identified and mobilization above this point is minimized to preserve blood supply to the anastomosis. The thoracic duct can be located at this level and ligated if desired.

**FIGURE 27-27** Left thoracoabdominal approach; delineate the circumferential diaphragmatic incision as well as the hiatal margin incision. A Penrose drain encircles the esophagus above the tumor.

The incision permits excellent exposure of the short gastric vessels, which are ligated starting at the hiatus. Care is taken along the greater curvature, where the short gastric vessels end and the right gastroepiploic vessel begins.
The right gastroepiploic artery is preserved. The gastrohepatic ligament is divided. The left gastric artery is identified and all celiac lymph nodes are swept up onto the specimen. The stomach is retracted anteriorly and the left gastric artery is divided with a vascular endoscopic stapler. The gastric tube is constructed by sequential fires of GIA staplers starting at the fundus and extending down to the crow’s foot of veins. Six centimeters of distal margin is desirable. A Kocher maneuver and pyloroplasty or pyloromyotomy are performed, and the tube is passed through the enlarged hiatus into the chest. The anastomosis is typically constructed inferior to the aortic arch and may be hand-sewn as described in the previous section or stapled.

If needed, the dissection can be carried to the neck with this incision with some difficulty. The proximal esophagus can be dissected bluntly under the aortic arch, and provided the neck has been prepped into the field, a left cervical incision is made as in the tri-incisional technique and the conduit pulled into the neck. Closure begins with careful reapproximation of the diaphragm with interrupted horizontal mattress 0 silk sutures followed by solid reapproximation of the costal margin with figure-of-eight wire or heavy nonabsorbable suture such as no. 1 Prolene. Some surgeons prefer not to divide the costal margin, and instead perform all intra-abdominal work through the divided diaphragm.

**ALTERNATIVE METHODS OF RECONSTRUCTION: COLON AND JEJUNUM**

**Colonic Interposition**

The stomach is the preferred organ for esophageal replacement because of its blood supply, the resistance of these vessels to atherosclerotic disease, the need for a single anastomosis, and the ability of the stomach to reach the neck without difficulty. Prior gastric surgery, scarring from peptic ulcer disease, or involvement with tumor may preclude use of the stomach as a conduit. In this instance, colon interposition may be employed. The left colon is preferred over the right colon for several reasons. Its diameter more closely resembles that of the esophagus, its vascular supply has less variation, and greater length can be obtained. Unfortunately, atherosclerotic disease most
commonly affects the inferior mesenteric artery, and the left colon is often more affected by diverticular disease than the right.

Preoperative preparation includes colonoscopy or barium enema to ensure normal anatomy and the absence of any intrinsic colonic disease. Patients older than 40 years or any patients with atherosclerotic risk factors should undergo mesenteric angiography. Significant vascular disease of the conduit vessel would preclude its use as a conduit. A complete bowel prep and oral antibiotics are necessary prior to operation.

LEFT COLON

After completion of the thoracic phase of the operation, the patient is placed in the supine position and a midline laparotomy is performed. After a careful search for metastatic disease, the left colon is mobilized by dividing the white line of Toldt and by dividing the attachments to the spleen and omentum. The colon is freed proximal to the hepatic flexure. A careful inspection is made of the vascular supply, including the marginal artery of Drummond (Fig. 27-28). A pulse should be palpable in the left colonic artery as well as the marginal artery. The middle colic artery supplying the hepatic flexure is clamped with a soft bulldog clamp and its perfusion is inspected for 10 minutes.
FIGURE 27-28 The mobilized colon is elevated, and the arterial supply and venous drainage are examined. The arterial and venous ligation sites and the mesenteric incision lines are illustrated for an isoperistaltic conduit based on a left colic artery supply.

Prior to conduit isolation, the GE junction is isolated and the cardia and lesser curvature are dissected with division of the phrenoesophageal ligament and the gastrohepatic ligament. The stomach is divided using a GIA stapler. A pyloric drainage procedure is performed. The length of colon needed is estimated by placing an umbilical tie along the proposed route of colonic interposition. This tie is placed alongside the colon and the length of required colon is determined.

After ensuring adequate blood supply to the conduit, the marginal artery is
ligated distal to both branches of the left colic artery. The middle colic artery is divided near its origin. The mesentery is scored and divided between clamps. The colon is divided with GIA staplers and the conduit is packed in moist gauze. The colocolonic anastomosis is most easily stapled in side-to-side functional end-to-end fashion. The mesenteric defect is closed with a running suture to avoid internal herniation. The esophagus is identified in the neck and the esophagectomy is completed as previously described in the tri-incisional esophagectomy section.

The colon can be brought to the neck via either the anterior mediastinum (substernal) or the in situ route (bed of the resected esophagus). The in situ route is preferred, as it provides the shortest route to the neck (Fig. 27-29). In instances of prior infection or scarring (as seen with gastric conduit necrosis or leak), the in situ route may be scarred and unusable. The substernal route may then be used with resection of the manubrium required to prevent acute angulation and possible obstruction in the neck. The colon is oriented in isoperistaltic position and drawn to the neck in an endoscopic camera bag as described previously. The proximal anastomosis is most easily performed using a single-layer interrupted technique with fine 4-0 silk sutures. An EEA or functional end-to-end stapled anastomosis is also acceptable. The nasogastric tube is guided through prior to completion of the anastomosis. The cologastric anastomosis is then performed onto the posterior aspect of the stomach. The easiest method of anastomosis employs an EEA stapler. The handle is placed through an anterior gastrotomy and creates the anastomosis in the posterior wall of the stomach. The gastrotomy is then closed with a TA stapler. The nasogastric tube must be guided through the anastomosis into the stomach. Any excess length in the conduit should be pulled into the abdomen; if it remains in the chest, obstruction may result. The colon is sutured to the left crus of the diaphragm at the hiatus using seromuscular sutures in a two-third circumferential fashion in order to prevent herniation of abdominal contents into the chest.
FIGURE 27-29  Lateral view of the colonic conduit in the posterior mediastinal esophageal bed. Cervical esophagocolonic and posterior cologastric anastomoses are shown. *Inset:* Neck incision marked and left colon conduit mobilized on the anterior chest wall, based on the marginal artery pedicle of left colonic artery and placed in isoperistaltic position.

**RIGHT COLON**

There are numerous conditions that may make the left colon unsuitable as a conduit, including extensive diverticular disease, stricture from ischemia or infection, atherosclerotic occlusion of the inferior mesenteric artery, or splenic vein thrombosis and thrombosis of the inferior mesenteric vein. In these instances, the right colon may be used as a conduit to reach the neck. The right colon is mobilized by lysis of its retroperitoneal attachments. The length of colon needed is estimated with an umbilical tape as described previously. The greater omentum is removed from the hepatic flexure and proximal half of the transverse colon. Its mesentery is transilluminated revealing the ileocolic, right colic, middle colic, and marginal arteries. The ileocolic and right colic arteries are clamped in preparation for division of these vessels and mobilization of the conduit based on the middle colic
artery. If perfusion appears adequate, these vessels are ligated. The peritoneum overlying the base of the mesentery is scored, and the remainder of the mesentery is divided between clamps and ligated. The proximal and distal ends of the conduit are divided with a linear cutting stapler. Some surgeons incorporate the ileocecal valve and distal ileum in the conduit because the diameter of the ileum closely approximates that of the esophagus. Others prefer not to use distal ileum in the anastomosis, as the valve may contribute to dysphagia.

The colocolonic anastomosis is performed with staplers. The right colon conduit is then rotated in clockwise fashion (as the surgeon looks into the abdomen) in preparation for isoperistaltic transfer into the chest. As stated earlier, the preferred route is via the esophageal bed. This route is often unavailable for use in colon transposition, as one of the most common indications is a failed gastric conduit placed in the esophageal bed. The retrosternal route is most often used. The diaphragm is bluntly detached from its inferior sternal attachments, and blunt dissection with the hand is performed to enlarge the tract. Division of cartilaginous attachments behind the manubrium is also necessary. The conduit is drawn into the neck via a plastic endoscopy bag as described previously. If the thoracic inlet is thought to be too constricting, the head of the clavicle, manubrium, and anterior aspect of the first rib may be resected. The proximal and distal anastomoses are performed as described for left colon conduits. The conduit may also be passed to the neck via the transpleural or subcutaneous route (with great cosmetic deformity).

**Jejunal Interposition**

Jejunal interposition may be applied as a free graft, pedicled graft, or Roux-en-Y replacement. Jejunum is often the third choice (after stomach and colon) for esophageal replacement, because it cannot replace the entire esophagus to the neck, but can be used to replace a portion of the distal or proximal esophagus. When distal esophagectomy is necessary for peptic stricture, jejunum or colon interposition is preferred, as both conduits are relatively resistant to reflux. The isoperistaltic conduits are believed to have a lower incidence of recurrent reflux than the simple gastric pull-up procedure. Free jejunal grafts are used in limited reconstructions of the cervical esophagus. Patients undergoing jejunal interposition should receive preoperative
antibiotics. Although a mechanical bowel preparation is not needed, it should be used if it is possible that colon may be needed.

**ROUX-EN-Y REPLACEMENT**

Roux-en-Y replacement is most commonly used after total gastrectomy and distal esophagectomy (Fig. 27-30). Unlike stomach, it will not reliably reach to the cervical esophagus. The jejunum is divided approximately 20 to 30 cm beyond the ligament of Treitz. The jejunum and its mesentery are held up and its arcade is transilluminated. The proposed point of division is identified, as are the mesenteric vessels to be divided. The first few arcades are not divided to preserve blood flow to the native jejunum. Up to 60 cm of jejunum can be mobilized using this technique. The mesentery is scored and these vessels are clamped near their origin from the superior mesenteric artery with soft bulldog clamps. The conduit is observed for about 10 minutes for evidence of ischemia. The vessels are then ligated and divided. A hole is made in the transverse mesocolon to the left of the middle colic artery, just large enough to pass the jejunum and its mesentery. For replacement after total gastrectomy, the proximal anastomosis is made to the very distal esophagus in the upper abdomen. If resection of the distal esophagus is required, the incision is usually extended across the costal margin to the sixth or seventh interspace. If additional length is needed on the conduit, the next vessel in the arcade is identified, test-clamped, and then divided. The anastomosis can be performed by stapled or hand-sewn technique. The stapled anastomosis is most easily performed with an EEA stapler. The largest EEA stapler possible should be used for the anastomosis. The distal esophagus may first be dilated with a lubricated metal dilator. A full-thickness 2-0 Prolene suture is used to create a purse string in the distal esophagus. The shaft may be introduced by opening the stapled end of the jejunum. It can then be passed out the side of the jejunum and united with the anvil. Care must be taken not to occlude the ongoing lumen of the jejunum with the stapler. Two full-thickness anastomotic doughnuts should be verified. After removing the stapler, the jejunal end is closed with a TA 60 stapler. A hand-sewn anastomosis in one or two layers can also be performed. The jejunum is tacked to the hiatus at several points using interrupted silk sutures. This prevents herniation of abdominal contents into the chest and limits tension on the esophagojejunal anastomosis. Likewise, defects in the colonic mesentery should be closed to
prevent an internal hernia. The distal anastomosis can be hand-sewn or more rapidly performed with a side-to-side functional end-to-end stapled anastomosis.


**PEDIRED JEJUNAL INTERPOSITION**

Pedicled jejunal interposition is most often used to replace a strictured distal esophagus (Fig. 27-31). A left thoracoabdominal incision is employed with a left seventh interspace incision extended across the costal margin and rectus muscle. The jejunum is transilluminated and an appropriate length of jejunum is selected, beginning 20 cm beyond the ligament of Treitz. A single large vessel is chosen as the conduit feeder vessel. The jejunum is transected
proximally and distally using a GIA stapler, and the mesentery is divided down each side toward the feeder vessel (Fig. 27-32A). The jejunum is reconnected using a side-to-side functional end-to-end stapled anastomosis (Fig. 27-32B). The pedicled jejunum is tunneled through the colonic mesocolon and brought up to the left chest through an enlarged hiatus. (Fig. 27-33) The proximal anastomosis can be constructed with an EEA stapler (usually 28 cm in size, but a larger anastomosis may be more resistant to postoperative stricture). The jejunogastric anastomosis is easily performed using an EEA stapler (inserting the handle through a separate gastrotomy). A two-layered hand-sewn anastomosis may also be used.

**FIGURE 27-31** Pedicled jejunal replacement of the distal esophagus. The
jejunum is brought through an incision in the transverse mesocolon.

**FIGURE 27-32** A. The jejunum is prepared in an isoperistaltic fashion (arrows) based on a distal mesenteric branch and proximal marginal arcade. The *dotted line* illustrates the line of resection of mesentery and the division of vessels. B. After dividing the mesentery and preserving the pedicle, jejunal continuity is restored and the mesenteric defect closed.
**FIGURE 27-33** Jejunal interposition graft to reconstruct the lower esophagus. An end-to-side esophagojejunostomy is performed to avoid tension on the vascular pedicle. A posterior jejunogastric anastomosis avoids tortuosity of the conduit while an 8- to 12-cm segment of the jejunal graft situated below the hiatus aids in the control of reflux.

**FREE JEJUNAL TRANSFER**

Free jejunal transfer is needed if the pedicle is not of sufficient length, such as in replacement of a portion of the cervical esophagus for benign disease. It is not clear whether use of a free jejunal transfer is preferable to total esophagectomy and gastric pull-up. The use of jejunum does carry a lower
incidence of postoperative reflux and avoids dissection of the thoracic esophagus; however, there is increased risk of graft ischemia and gangrene. Two anastomoses are required and there is an increased risk of anastomotic leak. As with a pedicled jejunal graft, a short segment of jejunum is chosen for harvest. A left cervical incision is made, and the esophagus as well as the carotid artery and jugular vein are isolated. A dominant feeder vessel in the jejunal segment is identified and divided with a scalpel. The artery and vein are flushed with heparinized saline. The proximal anastomosis is constructed first and is performed with a two-layer end-to-side hand-sewn anastomosis. An operating microscope is then used to perform the arterial and venous anastomosis to the carotid artery and jugular vein with 9-0 or 10-0 Prolene suture. The distal anastomosis is then performed in a fashion identical to the proximal anastomosis (Fig. 27-34). Typically, a meshed skin graft is placed over the conduit for continuous postoperative monitoring. A feeding jejunostomy tube is placed as with every case of esophageal replacement.
**FIGURE 27-34** Free jejunal graft used as a cervical esophageal replacement. It is typically covered with a meshed skin graft so that conduit health can be observed postoperatively.

**COMPLICATIONS AND HOW TO AVOID THEM**

**Anastomotic Leak**

The incidence of anastomotic leak is higher following cervical anastomosis (10%-17%) than intrathoracic anastomosis (5%-10%). The incidence of leak is believed to be higher in the cervical position for several reasons. First, increased length is needed and this may place increased tension on the anastomosis. The tip of the stomach, which is used in the cervical anastomosis, may have a more tenuous blood supply, as it is farther from the gastroepiploic artery. Additionally, venous engorgement due to a tight thoracic inlet may impair blood supply. An analysis of anastomotic leaks found that albumin level below 3 g/dL, positive margins, and cervical anastomosis were risk factors for anastomotic leak following esophagectomy. A randomized comparison of hand-sewn versus stapled anastomosis in 102 patients undergoing Ivor Lewis esophagectomy did not show any significant difference in the incidence of anastomotic leak. The incidence was 5% after a single-layer monofilament anastomosis and 2% after a stapled anastomosis. The incidence of leak following hand-sewn anastomosis is more operator-dependent, and those who perform few of these procedures may wish to use a stapled technique.

Anastomotic leak following Ivor Lewis esophagectomy is a feared complication that in the past was associated with a 50% mortality rate. Centers that routinely employ this technique have refined their techniques, resulting in very low leak rates in the 2% range. Early detection and aggressive management can reduce the high mortality rate usually associated with this complication. Unexplained fever, elevated white cell count, respiratory failure, delirium, hypotension, or low urine output may signal the onset of an intrathoracic leak. Confirmation is usually possible by Gastrografin swallow or instillation of contrast through the nasogastric tube.
Immediate intervention is required, and attempts at direct repair with muscle flap reinforcement and wide drainage are often successful. Patients who are unstable or severely ill should be diverted with a spit fistula, and either excluded at the hiatus or have the conduit closed and returned to the abdomen. In rare instances, a clinically silent, small, contained leak that is not adjacent to vital structures such as the trachea or aorta may be observed and treated with strict NPO status and enteral feeds.

Although leak is more common following cervical anastomosis, it is rarely life threatening. Occasionally a cervical anastomosis may leak into the chest and must be treated like an intrathoracic leak. Initially, mortality from a cervical leak was estimated at 20%, though recent series have shown that the mortality is much lower. Cervical anastomotic leak is usually signaled by fever, erythema, and fluctuance in the neck incision. Opening of the neck incision and probing down to the prevertebral fascia (with placement of a drain) is usually all that is needed. Patients can be allowed clear liquids by mouth and may be fed via jejunostomy tube until the leak is sealed. Barium swallow following esophagectomy may miss 10% of cervical leaks. Giving patients purple grape juice to drink and observing the drain during swallow may detect leaks missed by barium swallow.

**Anastomotic Stricture**

The same risk factors that predispose to anastomotic leak also predispose one to stricture. Indeed, it is very common to present with stricture following treatment for an anastomotic leak. Retrospective meta-analyses have shown that the incidence of stricture is higher after cervical reconstruction (28%) than after Ivor Lewis reconstruction (16%). The definition of stricture is not precise and is usually determined by the need for intervention (ie, dilation). As some surgeons are more aggressive than others with regard to dilation, this value may be misleading. A retrospective analysis of transhiatal esophagectomy patients revealed that the use of a stapled anastomosis, anastomotic leak, and the presence of cardiac disease were the only risk factors associated with the development of stricture. Other studies have mentioned intraoperative blood loss and poor conduit vascularization as risk factors. A unifying theme in anastomotic stricture (other than mechanical stapler issues) is impaired blood supply to the region of anastomosis. In an
effort to avoid ischemia, it is wise to not place the anastomosis too close to the tip of the gastric conduit. Careful handling of the gastroepiploic artery, ensuring systemic oxygen delivery, and avoidance of congestion all are important in avoiding anastomotic leak and stricture.

Mechanical factors may also contribute to development of stricture, especially when an EEA-stapled anastomosis is performed. In a randomized evaluation of the EEA stapler for Ivor Lewis anastomosis, the incidence of stricture was found to be 40% with a stapled anastomosis versus 9% with a hand-sewn anastomosis. When a small (25-mm) EEA stapler was used, the incidence of stricture was 43% as opposed to a 12.5% incidence with a 29-mm stapler, and no strictures were seen with a 33-mm stapler.\textsuperscript{47}

Postoperative strictures may nearly always be managed by bougie dilation. Repeat dilations are often needed. In the aforementioned study of strictures following Ivor Lewis esophagectomy, 53% of patients needed one dilation, 20% required two, 12% required three, and 8% required four. No patient was treated with reoperation. In Honkoop and associates’ study of anastomotic stricture following transhiatal esophagectomy, the average patient required three dilations to achieve normal swallowing. Perforations occurred in 2 of the 519 patients requiring dilation.\textsuperscript{49}

**Recurrent Laryngeal Nerve Injury**

The clearest risk factor for recurrent nerve injury is cervical anastomosis. In retrospective analyses by both Rindani et al. and Boshier et al., the incidence of recurrent nerve injury with a cervical anastomosis was double (11%) than that for intrathoracic anastomosis (5%)\textsuperscript{38,39} The recurrent nerve can be injured at any point, from its “recurrence” from the vagus nerve (around the subclavian artery on the right and around the aortic arch on the left), to its course in the tracheoesophageal groove, to its insertion into the larynx. Although an Ivor Lewis resection should not touch the recurrent nerve, traction or cautery injury to the vagus nerve may cause injury to the recurrent nerve.

A left neck incision is often used to approach the cervical esophagus. The right recurrent nerve is farther from the esophagus than the left, and it is easier to avoid the right nerve from a left neck incision than it is to avoid the left nerve from a right neck incision. During neck dissection, it is important
to stay immediately against the esophagus in order to avoid injury to the nerve. In a review of tri-incisional esophagectomy by Swanson and colleagues, refinements in technique resulted in a reduction of recurrent nerve injury from 14% to 7%. In the Brigham and Women’s Hospital technique, the vagus nerves are divided at the level of the azygos vein, and cranial dissection of the esophagus proceeds within the nerves. A Penrose drain is used to surround the esophagus and is positioned in the neck for later retrieval during the cervical phase of the operation to ensure isolation of the esophagus inside the recurrent nerves.

Early recognition and aggressive treatment are necessary to minimize respiratory complications from recurrent nerve injury. Recurrent nerve injury prevents cord apposition, making an effective cough impossible and interfering with protective reflexes involved in swallowing. Hoarseness is present with recurrent nerve injury but may be present after any intubation. Loss of effective cough is another hallmark of recurrent nerve injury but may not be present immediately following extubation, because there may be swelling of the cords after use of a double-lumen tube, a prolonged operation, and large fluid shifts. Effective cough may be lost between 24 and 48 hours after extubation as cord swelling decreases. Any patient with hoarseness and ineffective cough should undergo fiberoptic laryngoscopy. Immediate injection of the affected cord with gelfoam will allow an effective cough and clearance of secretions.

**Respiratory Complications**

In early series, anastomotic leak and infection were the most common cause of death following esophagectomy. In modern series, the most common cause of death is respiratory failure. The incidence of pneumonia following esophagectomy ranges from 2% to 57%. The assumption that the incidence of pneumonia is higher with transthoracic esophagectomy than with transhiatal esophagectomy has not been definitively borne out by the literature. A large meta-analysis by Rindani and coworkers showed no difference in incidence of pneumonia between the two techniques. Conversely, a more modern yet sizable meta-analysis of studies published between 1980 and 2006 did report a significantly higher incidence in pneumonia in the transthoracic group (21% transthoracic vs 17% transhiatal).
The authors, however, performed a subgroup analysis of 16 studies published after 1999, and this analysis no longer returned a significant difference in pneumonia between the two approaches. Two randomized trials, one by Goldmine and associates and one by Chu and colleagues, also showed no difference in the incidence of pneumonia. A larger randomized trial comparing tri-incisional, en bloc esophagectomy with transhiatal esophagectomy did show a higher incidence of combined atelectasis and pneumonia in the tri-incisional group (57%) versus the transhiatal group (27%). The unexpectedly high incidence of pulmonary complications in the transthoracic group should, however, be questioned, as reported rates are typically around 20% to 35%.

A variety of modifications and maneuvers can be employed to limit the incidence of pulmonary complications. All efforts must be made to spare injury to the recurrent nerve, and if injured, aggressive intervention including cord medialization is necessary. Efforts at limiting pain associated with thoracotomy, including a limited muscle-sparing thoracotomy, are helpful. The use of thoracic epidurals has been shown to decrease the incidence of pulmonary complications in thoracotomy patients. Early ambulation and aggressive pulmonary toilet are necessary.

**Bleeding**

Bleeding following esophagectomy occurs about 5% of the time regardless of the technique used. Meta-analyses have shown that estimates of blood loss are slightly higher with the transthoracic group as opposed to the transhiatal group. Preoperatively, antiplatelet agents should be stopped well in advance of surgery. Low-dose subcutaneous heparin or low-dose low-molecular-weight heparin should not increase the incidence of perioperative bleeding. Intraoperatively, arterial branches from the aorta to the esophagus should be clipped whenever possible. If blunt dissection is used, staying immediately against the esophagus should help avoid larger arteries, as the esophageal arterioles tend to form a fine plexus of vessels approximately 1 to 2 cm away from the wall of the esophagus. A notorious site of bleeding during the transhiatal dissection is the azygos vein or one of its branches. This bleeding usually occurs at about the level of the carina and, as always, extra care should be taken at this level. A common site of bleeding after any
thoracotomy is the chest wall itself, including intercostal vessels; these should be inspected after removing the retractor.

**Chyle Leak**

The thoracic duct enters the chest through the aortic hiatus and lies between the spine, azygos vein, and aorta at the level of the diaphragm. At approximately the T6 level, it crosses to the left side and eventually empties into the left subclavian vein. The incidence of chyle leak following esophagectomy ranges from 2% to 10% and is at greatest risk during en bloc resection. If the thoracic duct is taken during en bloc dissection, the duct is ligated at the hiatus and inspected for leak. It is wise to inspect the area of the thoracic duct at the end of any transthoracic dissection of the esophagus. Often, clear fluid (in the unfed patient) can be seen welling up in the area and may lead one to a laceration of the thoracic duct. In such instances, the leak should be repaired directly with pledgeted 4-0 Prolene sutures. Prophylactic ligation of the thoracic duct following esophagectomy is sometimes performed. In this maneuver, all tissues between the aorta, spine, and azygos vein at the level of the hiatus is ligated with a large (0 or 1) ligature.

The diagnosis of a thoracic duct leak should be suspected if chest tube output remains high (>800 mL/d) in a patient despite a normal volume status. Definitive diagnosis may be difficult, because chyle is not milky unless the patient has been fed fats. Fluid should be sent for Gram stain, triglyceride level, cell count, and cholesterol level. A triglyceride level greater than 1 mmol/L is strongly suggestive of a chyle leak, as is a lymphocyte count greater than 90%. If chylomicrons can be confirmed by electrophoresis, the diagnosis can also be established. A good bedside test involves feeding the patient cream enterally 200 to 300 mL over 2 hours and observing for a change in character of chest tube effluent, from serous to milky white.

Chyle leak following esophagectomy must be repaired. These patients are recovering from major surgery and most are malnourished. The loss of protein and lymphocytes associated with a chyle leak may be associated with infections and may interfere with healing. Once the diagnosis is confirmed, or even if it is strongly suspected, patients should be treated. They can be brought to the operating room and the thoracotomy incision reopened. The patient is given enteral cream 1 hour before the procedure to help locate the leak. The defect is repaired with a pledgeted 4-0 or 5-0 Prolene suture. A
careful inspection for other leaks should be performed before closure, and mass ligation of the duct at the hiatus should be considered as well.

CT- or MRI-guided noninvasive methods have been proposed for repairing chyle leaks. The cisterna chyli can sometimes be located under CT guidance, cannulated, and injected with either coils or glue. In a published trial of 42 patients (including 9 postesophagectomy patients), the thoracic duct could be embolized in 26, and 16 of these cases were cured.\textsuperscript{52}

**Impaired Conduit Emptying**

Numerous factors affect conduit emptying postesophagectomy. These include vagotomy, drainage through the pylorus, width of the conduit, redundancy and/or kinking of the conduit, and postoperative swelling. Studies objectively looking at conduit emptying following esophagectomy give conflicting results as to the effect of pyloroplasty on gastric conduit emptying time. A prospective trial studied 200 patients and randomized half to pyloroplasty and half to no pyloroplasty following Ivor Lewis esophagectomy.\textsuperscript{53} The average daily postoperative nasogastric drainage was no different between the two groups. Thirteen patients who did not undergo pyloroplasty had symptoms from delayed gastric emptying, and two died of aspiration pneumonia. There were no complications from the pyloroplasty procedure. Six months after the procedure, gastric emptying was 6 minutes in the pyloroplasty group versus 24 minutes in the group without pyloroplasty. These patients had more symptoms attributable to delayed emptying as well. The same group conducted a randomized trial of pyloroplasty versus pyloromyotomy and found both to be equally effective and safe.

Width of the gastric conduit may also affect emptying. A thin gastric tube has been shown to have a lower incidence of symptoms related to poor gastric emptying (3%) than patients either with the whole stomach (38%) or distal two-third stomach (14%) acting as the conduit.\textsuperscript{54} A conduit diameter of 5 to 6 cm is probably ideal. Excess conduit length or angulation may also impair emptying, and excess colon conduit length or angulation is known to cause immediate or delayed problems with emptying. However, a conduit that is too thin can lead to an increased anastomotic leak rate.\textsuperscript{55}
CONCLUSION

Esophagectomy can be a technically challenging operation. Mortality rates can vary greatly with experience. Hospital volume and surgeon experience play significant roles. Analysis of the relationship between volume and mortality shows a large variance in mortality from almost 25% in low-volume and low-experience centers to as low as 2.5% in high-volume centers. With improvements and increased penetration of minimally invasive techniques, mortality has been reported as low as 1.4%. Careful patient selection, preoperative preparation, and choice of operation, as well as meticulous surgical technique, excellent anesthetic and intensive care, and aggressive management of postoperative complications can limit the morbidity and mortality of this operation.

REFERENCES


It was a pleasure to receive a letter from Dr. Michael Zinner inviting us to write a prospective on the chapters from Drs. Daniel Tong and Simon Law from Hong Kong on cancer of the esophagus and Drs. Jon Wee, Shelby Steward, and Raphael Bueno from The Brigham and Women’s Hospital, Harvard Medical School, on surgical procedures to resect and replace the esophagus. We begin by stating both chapters are exceedingly well written, informative, and enlightening. Our reading identified areas where we were moved to comment based on our personal experience. The comments usually take the form of additional thoughts or alternatives. Occasionally, we raise a note of caution or take a controversial point of view.
THE PROBLEM OF BARRETT ESOPHAGUS

The specific reason for the dramatic increase in adenocarcinoma of the esophagus continues to remain a mystery, even though it represents the largest epidemiologic change ever recorded for a solid cancer. Reasons proposed for the significant and continuous increase in incidence of esophageal adenocarcinoma are the epidemics of obesity and gastroesophageal reflux disease (GERD). The latter can result in the complication of Barrett esophagus and its subsequent development into high-grade dysplasia. As Tong and Law point out, high-grade dysplasia is the last preinvasive stage in the metaplasia–dysplasia–cancer sequence and has become the focus of efforts to combat the problem. Intensive surveillance of patients with Barrett esophagus is proposed as a strategy to identify high-grade dysplasia prior to the evolvement of cancer and treat it with endoscopic mucosal resection or ablation. To date, the results of intensive surveillance have been disappointing, and the work involved in ablation and its required unlimited follow-up is extremely expensive. Further, Tong and Law indicate a 20% recurrence rate after an average follow-up of 2.4 years, and the median length of Barrett mucosa in which the recurrent lesion occurred was only 0.6 cm, which is significantly shorter and more difficult to identify than the pretreatment length.

Disappointment with intensive surveillance as a solution to the Barrett esophagus problem has stimulated an interest in the possibility of surgically preventing the development of Barrett esophagus. The progression of GERD to Barrett esophagus in patients who are receiving treatment with proton pump inhibitors (PPIs) has been reported by several investigators. This has led to concerns that PPI therapy does not address all aspects of the disease and patients who are at risk of progression need to be identified early in the course of their disease in order to prevent the development of visible Barrett esophagus. Recently, it has been reported that biopsies of the squamocolumnar junction that show microscopic intestinalized metaplastic cardiac mucosa in endoscopically normal patients with GERD are predictive of the evolvement of visible Barrett esophagus.

A further indicator of progression toward visible Barrett esophagus is a permanent structural alteration of the lower esophageal sphincter (LES) on manometry, resulting in uncontrollable reflux. Acid suppression therapy is
notably effective in patients who have a normal LES but less so in those who have a structurally defective LES. Permanent structural alterations of the LES are difficult to correct without surgical intervention. The likelihood of symptom control and prevention of progression to Barrett esophagus in patients with persistent symptoms on PPI therapy is greater if surgical correction of a compromised LES is carried out earlier rather than later.\textsuperscript{7}

A proposed solution to the rising incidence of esophageal adenocarcinoma is to apply the principle: Where there is no Barrett esophagus, there is no cancer. A competent Nissen fundoplication has been shown to prevent Barrett esophagus if performed before it develops.\textsuperscript{8} Early fundoplication in patients with microscopic intestinal metaplasia just below the squamocolumnar junction, in the absence of endoscopically visible Barrett esophagus, results in complete regression of the intestinal metaplasia and no evidence of visible Barrett esophagus in 74\% of patients.\textsuperscript{9} In a separate control group of patients with endoscopically visible Barrett esophagus, only 4\% of patients showed regression of the Barrett esophagus after fundoplication.\textsuperscript{9}

Despite the ability of the fundoplication to induce regression of microscopic intestinal metaplasia and prevent development of visible Barrett esophagus, the side effects of the procedure (ie, dysphagia, bloating, and the inability to burp and vomit) have discouraged the use of this approach to avert the evolvement of the precancerous lesion. Over the past decade, minimally invasive outpatient LES augmentation procedures have been developed. These procedures avoid the side effects associated with Nissen fundoplication and may therefore be appropriate for early surgical intervention.\textsuperscript{10} The effectiveness of these procedures to induce regression of microscopic intestinal metaplasia at the squamocolumnar junction and avert the development of Barrett esophagus and a subsequent adenocarcinoma should be investigated in future clinical studies.

The burden of esophageal adenocarcinoma is predicted to continue to rise dramatically in high-income countries.\textsuperscript{11} It is incumbent on both gastroenterologists and surgeons to work together to stop the rising incidence of Barrett esophagus, the premalignant lesion of esophageal adenocarcinoma. By 2030, it is predicted that 1 out of every 100 European men will be diagnosed with esophageal adenocarcinoma before the age of 75.\textsuperscript{11}
THE ERROR IN CLINICAL STAGING OF ESOPHAGEAL CANCER

Tong and Law have rightly pointed out that “accurate staging allows stage-directed therapies and quality control for clinical trials.” They could not be more correct; however, there is an emerging problem. Clinical studies based on clinical staging have up to an 84% error rate for specific staging of a patient\(^\text{12}\) and a 24% error rate for staging a patient above or below a specified stage.\(^\text{13}\) Such a degree of error could affect proper randomization between the arms of a clinical study if the size of the study population is insufficient. As a consequence, the results of randomized studies between different treatment regimens that are based on clinical staging become suspect.

Superficial esophageal adenocarcinomas, particularly T1a lesions, are nearly always staged correctly and cured by endoscopic mucosal resection. Similarly, advanced locoregional disease (cT2-3N2-3 in the updated staging system) is usually staged correctly, and although neoadjuvant therapy has been shown to be of benefit, cure of this advanced disease is rare. The problem with clinical staging arises in patients with limited locoregional disease (cT2-3N0-1 in the updated staging system) who fall between these 2 extremes. The accuracy of staging cT2-3N0-1 disease correctly by clinical staging is between 13% and 25%.\(^\text{12,13}\) In such patients, the assessment of nodal metastases remains problematic and is culpable for the staging error.

Complicating things further, it is now recognized that the number of involved lymph nodes is a critical factor in survival.\(^\text{14}\) The updated seventh edition of the American Joint Committee on Cancer (AJCC) staging system has N0 (no positive nodes), N1 (1-2 positive nodes), N2 (3-6 involved nodes), and N3 (7 or more involved nodes) categories. Currently, there is little information on the accuracy of clinical N staging using the updated staging system. Treatment algorithms would be simplified and clinical staging would be of little significance if neoadjuvant therapy was beneficial for all resected patients other than those with superficial tumors amenable to treatment by endoscopic resection alone. However, multiple studies have failed to show a benefit for neoadjuvant therapy in patients with limited locoregional disease.\(^\text{12,15-18}\)

A recent study by Worrell et al reported the accuracy of clinical staging and survival of patients treated with primary esophagectomy for limited
locoregional disease defined as cT1-3 and N0-1 (in the updated staging system, disease limited to 0-2 involved nodes).\textsuperscript{13} Using endoscopic resection, endoscopic ultrasound, and/or computed tomography/positron emission tomography scan, the final pathology confirmed accurate clinical staging (≤T3N1) in 76% of patients with limited locoregional disease. The remaining 24% of patients were understaged (>T3N1), and in all cases, understaging was based on advanced nodal (N2 or N3) disease. Overall, 65% of the patients were node negative (T1-2N0), and the survival rate in these patients was 82% at 5 years and would likely not have been improved with induction therapy. These results compare favorably to the 64% 5-year survival rate for similarly clinically staged patients who received neoadjuvant chemoradiotherapy before esophagectomy in a series reported from the MD Anderson Cancer Center.\textsuperscript{19} This comparison and other reported experiences are providing accumulating evidence that neoadjuvant therapy is not beneficial in node-negative patients.

There are now 2 studies that show the risk of systemic disease can be correlated with the number of involved lymph nodes and exceeds 50% when 3 or more nodes are involved.\textsuperscript{12,14} Consequently, it remains to be determined whether systemic induction therapy would be beneficial for patients with N1 disease (0-2 involved nodes based on the staging system) if they have less than a 50% chance of systemic disease recurrence.

In the study by Worrell et al 24% of patients were understaged, all on the basis of unsuspected N2-3 disease.\textsuperscript{13} The overall 5-year survival rate in correctly staged patients was 67%, compared with 33% for patients who were understaged ($P < .0001$). Consequently, understaged patients with advanced nodal disease are at high risk for systemic metastases, and resection alone is inadequate treatment.

Ideally, clinical staging would identify patients with advanced nodal disease so that they can be offered neoadjuvant therapy before resection. Toward this goal, Worrell et al performed a multivariable analysis on their studied population to identify independent factors that were statistically associated with an increased risk for nodal understaging. Three factors proved significant: dysphagia at presentation, tumor size >3 cm, and poor differentiation.\textsuperscript{13} When none of these factors were present, 97% of patients were correctly staged. Conversely, when all 3 factors were present, 92% of patients were understaged. Patients with 1 or 2 risk factors had an
intermediate risk of understaging. These findings suggest that, in addition to the results of imaging studies, these 3 factors can be used to select patients at high risk for nodal disease and for consideration of neoadjuvant therapy. Further, if these additional clinical factors are used, the number of understaged patients would be reduced from 24% to 12.5%. At this level, more definitive results of trials with neoadjuvant therapy would be forthcoming and help to properly select patients who should receive neoadjuvant therapy and those who should be protected from the potentially toxic and immunosuppressive effects of neoadjuvant therapy.

**CHOICE OF ESOPHAGECTOMY**

In their respective chapters, both groups of authors tackle the ongoing debate between transhiatal and transthoracic esophagectomy. Their discussions are excellent and point out the various factors to consider in choosing one or the other procedure. It is important to keep in mind that not all transthoracic esophagectomies are en bloc esophagectomies. Consequently, the basis for the debate between the 2 procedures is the principle that surgical cure of esophageal cancer is dependent upon early detection and complete surgical removal of all tumor and potential tumor-bearing lymph nodes. To appreciate the topic in both chapters, it is important for the reader to understand the historical development of the en bloc esophagectomy.

The en bloc esophagectomy was first described by Andrew Logan in 1963. The borders of Dr. Logan’s dissection were the esophageal hiatus and costovertebral angle inferiorly; the aorta and thoracic spine posteriorly; the trachea, pericardium, and diaphragm anteriorly; and the arch of the azygos vein superiorly. In the abdomen, the proximal stomach and greater omentum are removed along with the node-bearing tissue along the right crus, left crus, porta hepatis, portal vein, common hepatic artery, celiac artery, left gastric artery, splenic artery, and splenic hilum. Although the extensive procedure was effective in curing some patients with cancer of the esophagus, the rate of cure was barely more than the mortality of the procedure.

Early treatment paradigms viewed esophageal carcinoma as a systemic problem at the time of diagnosis. This encouraged the concept of palliation rather than cure as the goal of the surgical procedure and persuaded surgeons to perform the thoracic portion of the dissection from the abdomen through
the esophageal hiatus as a means of providing palliation with less morbidity and mortality. Other surgeons were performing the en bloc dissection for early cancers and reserving the palliative transhiatal dissection for more advanced disease in order to reduce morbidity and mortality when there was a low probability of cure. The policy of reserving the en bloc dissection for early cancers was first challenged in 1997 by David Skinner and colleagues. Their retrospective study showed the 4-year and overall median survival after an en bloc esophagectomy was significantly improved over that achieved with a more limited resection with no difference in mortality and morbidity. Some surgeons argued that the improvement was a result of selection bias because more patients with a lower stage were in the en bloc group. However, when patients with stage III disease were analyzed, there was a significant improvement in the 4-year survival of 11% after the limited resection compared to 34.5% after the en bloc resection.

As retrospective evidence in favor of the en bloc dissection was emerging, the controversy over the 2 techniques grew among surgeons, and the scientific community was encouraged to perform a robust randomized controlled trial comparing resection techniques. A flaw of this methodology was pointed out by Altorki and colleagues, when they stated that “a randomized trial, however, can only compare potentially comparable strategies. The unquestionable deficiency of limited resections in providing adequate staging will not vanish in a randomized setting.” This was proven by van Lanschot’s group in 2002, who performed a randomized controlled trial comparing transhiatal and en bloc resections in patients who were American Society of Anesthesiology (ASA) class I or II and did not receive neoadjuvant chemotherapy and/or radiation therapy. The en bloc patients had significantly more nodes resected than the patients who underwent transhiatal resection (median, 31 ± 14 vs 16 ± 9 nodes). Further, the patients who had the en bloc resection had more stage III and IV disease than those who had a transhiatal resection. Despite their advanced stages, the patients who had the en bloc resection were trending toward an improved 5-year disease-free survival compared to those who had the transhiatal dissection. The difference, however, was not statistically significant.

Because a randomized controlled trial is unable to make an appropriate comparison between resection methods due to the difficulty of having a population of patients with the same tumor stage, the next best method is a
matched comparison. This was done by Johansson and associates in 2004. They compared patients receiving transhiatal or en bloc R0 resection for T3 adenocarcinoma with at least N1 disease, ≥20 lymph nodes removed, and no neoadjuvant therapy. The patients were followed for a minimum of 5 years or until death from recurrent cancer. The only significant differences between the groups were median age (71 years for transhiatal vs 57 years for en bloc) and the median number of resected nodes (29 for transhiatal vs 52 for en bloc). The 5-year overall survival was improved with en bloc resection compared to transhiatal resection; however, the survival advantage was limited to patients with 8 or fewer positive nodes. All patients with evidence of 9 or more involved lymph nodes had a similar survival regardless of resection technique. On Cox analysis, only the number of involved lymph nodes and the type of resection were significant factors for improved survival.

In light of the evidence put forth by the report of Johansson et al in 2004, van Lanschot and associates reanalyzed their randomized study data to assess differences in survival by resection type and number of involved nodes. When this was done, those with 1 to 8 involved lymph nodes had an improved overall survival after an en bloc resection (39%) compared to those who had a transhiatal resection (19%). Patients who had an en bloc resection also had reduced locoregional recurrence rate (42% for transhiatal vs 25% for en bloc) and an improved 5-year disease-free survival (23% for transhiatal vs 46% for en bloc; \( P = .002 \)). Just as Johannsson’s report found in 2004, there were no survival difference between resection techniques in patients with 0 or ≥9 involved lymph nodes.

The proposed explanations for the poor survival of patients with 1 to 8 involved lymph nodes who had the transhiatal resection are as follows: (1) After a transhiatal resection, there remains more undetected patients with >8 involved lymph nodes; (2) the transhiatal resection is less able to remove involved lymph nodes in patients with ≤8 involved lymph nodes; and (3) a combination of both explanations. To investigate these possible explanations, a multinational study was performed in 2008 by Peyre and associates to determine if the number of involved lymph nodes could predict the risk of systemic disease after esophagectomy irrespective of the resection technique. The study showed that patients with systemic disease were more likely to have T3 tumors, and 3 or more involved lymph nodes. Patients with only 1 or 2 involved lymph nodes were significantly less likely to develop
systemic disease compared to patients with 3 to 7 involved lymph nodes (44% vs 69%, respectively; \( P < .001 \)). The relationship of nodal disease to systemic disease in this study indicated that when 3 or more nodes are involved, the likelihood of systemic disease is >50% and approaches 100% with 8 or more involved lymph nodes.

Based on the above studies, the goal to improve the survival of patients with esophageal cancer by surgery should be to remove all diseases in patients with <8 involved nodes. To determine how many nodes need to be resected at the time of surgery to accomplish this task was studied in a second trial by Peyre and associates in 2008.\(^{26}\) They identified the top 3 independent predictors associated with survival using Cox regression analysis. The number of involved lymph nodes was the strongest predictor of outcome, followed by the depth of invasion (T) and the total of number of nodes removed. A linear association with improved survival occurred with increasing number of lymph nodes removed. The resection that took out the maximal number of nodes was an en bloc resection, with a median of 30 nodes removed. In contrast, the median numbers of nodes taken out by other resection techniques were as follows: transhiatal, 12 nodes; Ivor-Lewis, 13 nodes; transthoracic, 13 nodes; and thoracoabdominal, 14 nodes. Of the 3 predictors of survival (ie, the number of involved nodes, the depth of tumor invasion, and the number of nodes removed), only the number of nodes removed can be influenced by the surgeon. To maximize the outcome of surgical resection for esophageal cancer, a lymphadenectomy that removes a minimum of 23 to 29 nodes needed to be performed.\(^{26}\) The operation most likely to achieve this threshold is an en bloc resection.\(^{26}\) In an era when esophagectomy can be performed safely, emphasis must now be placed on performing an adequate oncologic procedure. From a logical perspective, the en bloc resection appears to do this the best.

A study by Koenig and coworkers in 2009 showed that the reason for improved survival following the removal of more lymph nodes was the likelihood of taking out lymph nodes containing micrometastases.\(^{27}\) The lymph nodes containing micrometastases were identified by immunohistochemistry after a curative resection without neoadjuvant or adjuvant therapies. In patients with T2 or T3 disease, 36.8% had micrometastases, compared to 11% of patients with T1 tumors. The 5-year survival of patients with detected occult micrometastases in lymph nodes was significantly worse than that of patients without nodal micrometastases (30%
vs 76%, respectively). The en bloc resection achieves the highest number of lymph nodes removed, and as a consequence, it removes a greater number of lymph nodes containing micrometastases; for this reason, it is associated with a better survival.

Some may argue that with the use of neoadjuvant therapy and en bloc resection is not necessary. Rizzetto et al\textsuperscript{28} showed in a 2008 study that, in patients with locally advanced adenocarcinoma of the esophagus, all of whom were treated with neoadjuvant therapy, there was a significant improvement in overall survival and survival with residual disease in patients who underwent an en bloc esophagectomy compared to those who had a transhiatal resection. The study clearly showed that even after neoadjuvant therapy, the extent of resection is an important determinant of long-term survival from esophageal adenocarcinoma. The explanation for this finding relates to the higher locoregional failure rate with the transhiatal resection and likely to the removal of both known and unknown (micrometastatic) disease with the extended lymphadenectomy performed by the en bloc resection.

REFERENCES


STOMACH AND DUODENUM
INTRODUCTION

Most benign gastric disorders are either inflammatory or neoplastic. A variety of vascular, mechanical, congenital, and traumatic disorders also affect the stomach. Some of these are covered in other chapters of this book. Surgical management of benign gastric disorders has evolved significantly over the last 40 years. Elective peptic ulcer surgery for intractability has largely been replaced by medical management, though urgent operation for perforation is not uncommon, and occasional elective ulcer operation is still necessary for obstruction or nonhealing. Most elective (and even urgent) gastric procedures can now be performed with laparoscopy (and in some cases with robotic assistance) if local expertise is available. Intraoperative endoscopic guidance with or without ultrasound allows accurate lesion localization and can help the surgeon perform a more targeted resection when wide margins are not necessary.
**HELICOBACTER PYLORI INFECTION**

*Helicobacter pylori*–induced chronic gastritis is the most important risk factor for peptic ulcer and gastric adenocarcinoma, a major cause of cancer death worldwide. Successful *H pylori* treatment largely eliminates recurrent peptic ulcer in infected patients, and eradication of *H pylori* worldwide would eliminate most cases of gastric adenocarcinoma. *H pylori* infection is also associated with mucosa-associated lymphoid tissue (MALT) lymphoma, dyspepsia, hyperplastic gastric polyps, and even idiopathic thrombocytopenic purpura (ITP). When Marshall and Warren elucidated the relationship between *H pylori* and peptic ulcer disease, a discovery for which they were later awarded the Nobel Prize in medicine, they rekindled the hypothesis that this common clinical malady was an infectious disease. It is now clear that most gastric adenocarcinoma is also related to chronic *Helicobacter* gastritis.

*H pylori* is a gram-negative spiral flagellated organism that currently infects more than half of the people in the world. The prevalence of *H pylori* infection varies among populations and is strongly correlated with socioeconomic conditions. In a number of developing countries, *H pylori* infection affects more than 80% of middle-aged adults, and reinfection risk after curative treatment is high. Infection rates are lower in industrialized countries. Epidemiological data indicate that the prevalence of infection in the United States has been declining since the second half of the 19th century, with the decreases corresponding to improvements in hygiene and sanitation. Nonetheless, *H pylori* infection is predicted to remain endemic in the United States for the next century. Human beings are the only reservoir for *H pylori*. Infection is presumed to occur by oral ingestion of the bacterium. Family members of infected individuals are at increased risk of infection. In developing countries, most people become infected during childhood. A number of occupations also show increased rates of *H pylori* infestation, notably healthcare workers. Infection with *H pylori* is a chronic disease and does not resolve spontaneously without specific treatment. Worldwide, *H pylori*–induced gastritis accounts for 80% to 90% of all gastritis.

*H pylori* has evidently adapted to the hostile gastric environment and displays a number of features that permit its entry into the surface mucus layer, attachment to gastric epithelial cells, evasion of host immune responses, and persistent colonization of the surface epithelium and gastric
pits despite luminal acidity. Up to 15% of the protein in a *Helicobacter* organism is composed of cytoplasmic urease that converts periplasmic urea into CO$_2$ and ammonia, the latter buffering the surrounding acid. *H pylori* infection is not invasive of the gastric mucosa, and the host immune response is triggered by the attachment of bacteria to gastric epithelial cells. The initial inflammatory response is characterized by recruitment of neutrophils, followed sequentially by T and B lymphocytes, plasma cells, and macrophages. The resultant chronic gastric inflammation in affected individuals is characterized by enhanced mucosal expression of multiple cytokines and the presence of reactive oxygen and nitrogen species, and long-term infection is associated with mucosal cell DNA damage and chromosomal instability.

The relationship between *H pylori* infection and peptic ulceration is overwhelmingly strong and multiple observations establish *H pylori* as a factor in the pathogenesis of peptic ulceration. Unfortunately, an effective vaccine has not yet been developed. *H pylori* infection is invariably followed by the development of chronic gastritis, and the organism is the primary cause of chronic active gastritis worldwide. The infectious response to *H pylori* is characterized by non-erosive inflammation of the gastric mucosa. Antral gastritis is present histologically in patients with peptic ulcer, and *H pylori* can be isolated from inflamed gastric mucosa of ulcer patients. Postprandial hypergastrinemia and elevated basal acid secretion are common. Gastric metaplasia of the duodenal bulb develops after infestation of the antral mucosa. Metaplastic gastric epithelium in the duodenum is colonized by *H pylori* from gastric sources, and this gastric metaplasia is extremely common in duodenal epithelium surrounding areas of peptic ulceration. Eradication of *H pylori* with antibiotics that have no effect on acid secretion leads to ulcer healing, and treatment of peptic ulceration with bismuth compounds, which inhibit *H pylori*, is associated with reduced rates of ulcer relapse relative to acid suppression therapy. Relapse of duodenal ulcer after eradication of *H pylori* may be preceded by reinfection of the gastric mucosa by the organism.

However, it is clear that infection by *H pylori* alone does not cause peptic ulceration in most individuals, suggesting the existence of other pathogenetic factors. Up to half of patients evaluated for dyspepsia have histologic evidence of *Helicobacter* infection but no ulcer. In developed countries, one-fifth of healthy volunteers harbor the bacteria, and the incidence of bacterial
infestation increases with age in the healthy, asymptomatic population. The occurrence of peptic ulcers in only a fraction of individuals who harbor the organism suggests that other factors must also act to induce ulceration. Even in the presence of active *H pylori* infection, strong acid suppression usually heals peptic ulcer, an observation consistent with the old dictum “no acid, no ulcer.” However long-term proton pump inhibitor (PPI) use in patients with active *Helicobacter* infection is associated with corpus predominant gastritis, which leads to atrophic gastritis and increases the risk of gastric cancer.

Testing for *H pylori* infection should be performed in patients with peptic ulcer, gastritis, significant dyspepsia, MALT lymphoma, and early gastric cancer. Noninvasive methods for diagnosis of *H pylori* infection include the urea breath test, serology, and detection of stool antigen. The urea breath test is based on production of urease by *H pylori* in the gastric mucosa, and a positive test indicates active infection. C 14-labeled urea is ingested and C 14-labeled CO$_2$ is produced and excreted in the breath. This test has a sensitivity and specificity of greater than 90%. The urea breath test is useful for initial diagnosis of infection and for follow-up after eradication therapy, since unlike serology, it is positive only in the presence of active infection. The stool antigen test is another noninvasive test to detect active *H pylori* infection. Both polyclonal and monoclonal kits have been developed. Different kits are available for both outpatient and inpatient settings. These tests may perform differently in different geographic locations according to the antigenic composition of the circulating strains, so it is recommended that only locally validated tests be used. Because *H pylori* induces a strong immunologic response, serological testing is useful but may not be as accurate as the urea breath test or the stool antigen test, and a positive serology persists after eradication of *H pylori* infection. Consideration should be given to confirming a positive *H pylori* serology with another more accurate test. *H pylori* infection can also be diagnosed by histologic evaluation of gastric biopsies and/or the rapid urease test on fresh biopsies. Culture of *H pylori* is not routine and is usually reserved for recurrent infection and for antibiotic sensitivity testing when second-line therapy has failed. All of these tests for *H pylori* have a false negative rate.

Patients with a positive test should be treated, and in the appropriate clinical scenario, some patients with a negative test should probably be treated as well (unexplained gastritis; recurrent or intractable peptic ulcer). Documented eradication of *H pylori* infection is the goal of treatment in each
patient. An enormous worldwide experience has developed relating to \( H \) \textit{pylori} eradication. More than 2000 articles report the results of antibiotic trials, and a large number of summary articles and meta-analyses are available. It is important to note that none of the therapeutic regimens reported to date cure \( H \) \textit{pylori} infection in 100% of patients. To be effective, antimicrobial drugs must be combined with gastric acid secretion inhibitors or bismuth salts (Table 29-1). In the absence of treatment, eradication of \( H \) \textit{pylori} infection is very rare. The Maastricht V/Florence Consensus Report provides current recommendations for diagnosis and treatment of \( H \) \textit{pylori} infection in various clinical scenarios, including recommendations for areas with high metronidazole and clarithromycin resistance (Fig. 29-1). The United States currently demonstrates high clarithromycin resistance but low to intermediate metronidazole resistance, similar to the patterns for most of central and southern European countries. Ideally, a treatment regimen is chosen with 90% effectiveness, and repeat noninvasive testing to confirm eradication is performed. Treatment failure requires an alternative course of therapy. Failure to eradicate infection after two tries should prompt \textit{Helicobacter} culture and sensitivity testing, and referral to a specialist. With assiduous treatment, \textit{Helicobacter} eradication can be achieved in nearly every patient. Patients with atrophic gastritis require endoscopic surveillance.

| TABLE 29-1: COMMON TREATMENT REGIMENS FOR \( H \) \textit{PYLORI} |
Triple therapy (10-14 days)
  PPI BID  
  Amoxicillin 1 gm BID or metronidazole 500 BID  
  Clarithromycin 500 mg BID  

Quadruple therapy option 1 (14 days)\(^a\)  
  PPI BID  
  Bismuth subsalicylate 524 mg QID  
  Metronidazole 250 mg QID  
  Tetracycline 500 mg QID or doxycycline 100 BID  

Quadruple therapy option 2 (14 days)  
  PPI BID  
  Amoxicillin 1 gm BID  
  Metronidazole 500 BID  
  Clarithromycin 500 mg BID  

\(^a\)Recommended for failures of triple therapy and in areas with high *Helicobacter* resistance to clarithromycin.

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* High (>15%) clarithromycin resistance

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- Low metronidazole resistance
  - PPI-amoxicillin-metronidazole triple therapy

- Low dual clarithromycin and metronidazole resistance (<15%)
  - Bismuth quadruple or concomitant non bismuth containing quadruple therapy

- High dual clarithromycin and metronidazole resistance (>15%)
  - Bismuth-containing quadruple therapies\(^**\)

\* Regardless of their population expectations, individuals who have previously taken clarithromycin and/or metronidazole should be considered high-risk patients for dual resistance.

\** If bismuth is not available, levofloxacin, rifabutin and high dose dual (PPI + amoxicillin) therapies might be considered. If tetracycline is not available, bismuth-containing quadruple therapy combining furazolidone-metronidazole or amoxicillin-metronidazole can be considered.

**FIGURE 29-1** Treatment algorithm for *Helicobacter pylori* in areas with high clarithromycin resistance.
FUNCTIONAL DYSPEPSIA

Dyspepsia is a very common symptom complex characterized by pain and discomfort centered in the upper abdomen. Up to 50% of patients who present with dyspepsia may have *Helicobacter* infection, depending on the regional prevalence of the latter. Patients with dyspepsia and alarm symptoms require esophagastroduodenoscopy (EGD). Testing and treatment for *Helicobacter* should be considered. Functional dyspepsia is diagnosed when there are no endoscopic or histologic findings, or when chronic symptoms persist after *Helicobacter* eradication has been documented, but it is important to note that *Helicobacter*-associated dyspeptic symptoms may persist for a while after eradication. When a dyspeptic patient has no diagnostic workup, the condition is classified as “non-investigated dyspepsia.” For surgeons, the importance of non-ulcerative dyspepsia relates to its place in the differential diagnosis of epigastric pain. There is no role for surgery in the treatment of this disorder.

ATROPHIC GASTRITIS

Atrophic gastritis is characterized by shrinkage or disappearance of gastric glands along with loss of parietal and chief cells. By far the most common cause is chronic *H pylori* infection, particularly the corporal distribution (as opposed to the antral distribution, which is more typically associated with peptic ulcer disease). Autoimmune destruction of cells (pernicious anemia) and chemical irritation (eg, bile reflux) can also result in atrophic gastritis. Some patients with atrophic gastritis develop intestinal metaplasia in the gastric mucosa, which may progress to dysplasia and then to gastric cancer. Numerous cofactors have been implicated including diet, altered gastric microbiome, genetics, and hypergastrinemia. Patients with atrophic gastritis are at risk for gastric cancer and some warrant endoscopic surveillance. Patients with metaplastic atrophic gastritis are at higher risk for gastric cancer, and those with dysplastic metaplasia even higher. Patients with high-grade dysplasia may benefit from gastrectomy. The cancer risk is related to the extent of the atrophic gastritis and intestinal metaplasia, and grading systems have been developed to stratify cancer risk based on endoscopic findings. Two such systems are the operative link on gastritis assessment (OLGA) and the operative link on gastric intestinal metaplasia (OLGIM).
assessment. These systems define the severity (stage) of atrophic gastritis based on the histologic grading of at least five gastric biopsies (lesser and greater curve antrum; lesser and greater curve corpus; angularis incisura) (Table 29-2). Since pathologists are more likely to agree on the histological diagnosis of intestinal metaplasia than they are on atrophic gastritis, the latter tool (OLGIM) may be more useful in stratifying gastric cancer risk. Patients stratified as Stage 3 or 4 gastritis and those with pernicious anemia may benefit from surveillance endoscopy every 3 years. Serum markers are also useful in helping to identify patients with atrophic gastritis, who usually have increased serum gastrin and iron deficiency due to parietal cell loss and hypochlorhydria or achlorhydria, decreased pepsinogen I levels due to chief cell loss, and B₁₂ deficiency due to parietal cell loss and concomitant loss of intrinsic factor.

### PEPTIC ULCER DISEASE

#### Epidemiology

Peptic ulcer disease (includes duodenal, gastric, and marginal ulcers) is a major public health problem in the United States and a source of substantial health care expenditure (Table 29-3). Overall, peptic ulcer mortality and hospitalization rates have declined from over 200,000 admissions in 1993
down to about 150,000 in 2006. Hemorrhage continues to be the most frequent presentation at hospital admission, followed by perforation and obstruction, but perforation is by far the most common indication for operation nowadays. Currently bleeding peptic ulcer is typically treated successfully with endoscopic techniques, occasionally with help from interventional radiology, and emergency operation for bleeding is unusual. Although overall mortality rates in patients hospitalized for peptic ulcer decreased slightly (2.7%, down from 3.8%), no change was seen in the determinants of mortality. Perforation is still associated with the highest mortality, followed by obstruction and then bleeding. The mortality from surgical intervention decreased over the time period but remains high compared to endoscopy and embolization. In parallel with the discovery of *H pylori* and the subsequent development of improved therapies for its eradication, surgical treatment of peptic ulcer has changed dramatically, with the virtual elimination of elective operations for intractable peptic ulcer disease. Operative therapy is now used mostly for urgent or semi-elective treatment of complications from the disease; ie, perforation, obstruction, bleeding, and rarely nonhealing.

**TABLE 29-3: HOSPITALIZATION FOR PEPTIC ULCER IN USA 2006** *(NATIONAL INPATIENT SAMPLE)*
Pathophysiology

The pathogenesis of peptic ulceration is multifactorial but increasingly understood to be a consequence of *H pylori* infection and nonsteroidal anti-inflammatory drug (NSAID) use. Before recognition of the role of *H pylori*, ulcer disease was conceived as an imbalance between acid and pepsin secretion and mucosal defense, with the balance shifted toward peptic injury and disease. In groups of patients, increases in acid secretion are well documented, and although gastric acid is crucial in the development of ulcers, an acquired defect in mucosal defense exists to tip the balance away from health. Mucosal infestation of the antrum with *H pylori* is the factor that contributes to ulceration in most patients both by weakening local defenses and increasing acid secretion. Aspirin and NSAID use is the second most important factor in ulcer pathogenesis, largely via weakened mucosal defenses. Other factors such as exogenous steroids and acute stress undoubtedly play a role in ulcer formation (Table 29-4). Substantial evidence implicates cigarette smoking as a significant risk factor in the development of
chronic peptic ulcers. Smokers appear to have an increased risk of developing \textit{H pylori} infection relative to nonsmokers. Cigarette smoking impairs ulcer healing and increases the risk of recurrent and/or marginal ulceration. Continued smoking blunts the effectiveness of active ulcer therapy. Cigarette smoking increases both the probability that surgery will be required and the risks of operative therapy. When \textit{H pylori} is eradicated in smokers, they appear to have no greater risk of peptic ulceration than nonsmokers. This observation suggests that smoking is probably not an independent risk factor for ulcer disease but acts by increasing the harmful effects of bacterial infection. Cessation of smoking is a key goal of anti-ulcer therapy.

### TABLE 29-4: RISK FACTORS FOR DEVELOPMENT OF PEPTIC ULCER

- \textit{Helicobacter pylori} infection
- NSAID and aspirin use
- Smoking
- Increased acid secretion
  - Gastrinoma
  - Retained antrum
  - Prolonged fasting
- Stress
  - Neurologic (“Cushing ulcer”)
  - Burns (“Curling ulcer”)
  - ICU (“stress ulcer”)
  - Psychologic stress
- Ischemia
  - Cocaine and methamphetamine use
  - Roux limb
  - VEGF inhibitors; eg, Bevacizumab
- Steroids

Abnormalities of gastric acid secretion in patients with peptic ulceration have been recognized for more than 50 years. The formation of peptic ulcers clearly depends on gastric secretion of acid and pepsin. This association is emphasized by the dictum “no acid—no ulcer,” and \textit{H pylori} infection is known to secondarily induce alterations in gastric acid secretion.
Abnormalities of mucosal function have been invoked as contributing factors to peptic injury. In support of this concept, several agents that are used to treat peptic ulceration are cytoprotective. The ability of such agents to heal ulcers suggests that abnormalities in mucosal defense, in addition to abnormalities in acid secretion, cause ulceration. Most cytoprotective agents act via mucosally secreted bicarbonate or on mucosal prostaglandin production.

NSAIDs are a major risk factor for the development of acute ulceration and for hemorrhagic complications of ulceration. NSAIDs produce a variety of lesions, ranging from superficial mucosal erosions to deeper ulcerations. While the mucosal injury caused by NSAIDs is more common in the stomach than in the duodenum, ulcer complications occur with equal frequency in these two sites. *H pylori* and NSAID use independently increase the risk of peptic ulcer and ulcer bleeding. These agents also act synergistically. In the duodenum, it appears likely that invasive *H pylori*–associated ulcers are compounded by the direct injurious effects of NSAIDs. The injurious actions of NSAIDs are secondary to suppression of prostaglandin production. Numerous experimental models have demonstrated that NSAIDs injure the gastroduodenal mucosa. Ulcers resembling those occurring in humans can be produced by administration of NSAIDs to animals, and NSAID-associated gastric ulcers can be prevented by the coadministration of prostaglandin analogues. Ulcers associated with NSAIDs heal rapidly when the drug is withdrawn, corresponding temporally to reversal of antiprostaglandin effects. Clinically significant ulceration of the stomach and duodenum is estimated to occur at a rate of 2% to 4% per patient-year in NSAID users. The risks of long-term NSAID use are increased by *H pylori* infection and cigarette smoking. The incidence of NSAID-related ulcer complications is highest in older patients, as is attendant mortality rate. Peptic ulcer disease is rare in individuals who are *H pylori*–negative and who do not receive NSAID medications.

**Diagnosis**

Peptic ulceration is typically characterized by nonradiating epigastric pain described as burning, stabbing, or gnawing. Referral of pain to the back may indicate posterior penetration of the ulcer. The pain is usually related to eating, with duodenal ulcer pain relieved by eating, which sometimes makes
gastric or marginal ulcer pain worse. Ingestion of antacids or initiation of antisecretory agents (H2 antagonists or PPIs) usually provides prompt relief. In uncomplicated cases, physical examination is usually normal. The differential diagnosis includes a variety of diseases originating in the epigastrium and upper GI tract. Common disorders to be distinguished include non-ulcer dyspepsia, gastritis, gastric neoplasia, cholelithiasis and related diseases of the biliary system, neoplastic lesions of the liver, and both inflammatory and neoplastic disorders of the pancreas. In dyspeptic patients, especially those older than 50 years of age, the most important differential diagnoses are peptic ulceration and gastric cancer.

The evaluation of patients with suspected peptic ulceration usually involves endoscopic examination of the esophagus, stomach, and duodenum. In controlled trials, endoscopy was both more sensitive (92% vs 54%) and more specific (100% vs 91%) than radiographic examination, but the latter should be considered if perforation is suspected. The most frequent site for duodenal peptic ulceration is the first portion of the duodenum, with the second portion less frequently involved. Peptic ulceration of the third or fourth portions of the duodenum is distinctly unusual and raises the possibility of gastrinoma or nonpeptic causes of ulceration such as cancer or ischemia. Peptic ulcers in the pyloric channel or the prepyloric area are similar in appearance to duodenal ulcers and should be treated as such (type 3 gastric ulcers). Endoscopic demonstration of a duodenal ulcer does not require duodenal biopsy but should prompt mucosal biopsy of the gastric antrum to demonstrate the presence of *H pylori* and guide subsequent therapy.

**Peptic Ulcer Location**

The three typical locations for peptic ulcer are duodenal, gastric, and marginal or anastomotic, and the pathophysiology and treatment vary by location. In the United States, benign gastric ulcers are found in approximately 90,000 new patients a year, about one-fifth that of duodenal ulceration. The opposite is found in Japan, where gastric ulcers are 5 to 10 times more common. Gastric ulcer is more common in men than women and occurs in a patient cohort approximately 10 years older than that of duodenal ulceration. In symptomatic patients, upper GI endoscopy is the preferred method for diagnosing peptic ulcers, though radiologic studies are often
complementary. About 10% of gastric ulcers are malignant or associated with malignancy, so aggressive biopsy and brushings, as well as careful follow-up to demonstrate healing, are mandatory. All gastric ulcers should undergo multiple biopsies, obtained from the perimeter of the lesion. The addition of endoscopic brushings to multiple biopsies increases diagnostic accuracy to approximately 95%. Although benign gastric ulcers may occur in any location in the stomach, more than half are located along the lesser curvature proximal to the incisura angularis. Fewer than 10% of benign ulcers are located on the greater curvature. Most benign gastric ulcers lay within 2 cm of the histologic transition between fundic and antral mucosa. Gastric ulcers are classically categorized as type 1 (lesser curvature near angularis incisura), type 2 (gastric ulcer associated with active or inactive duodenal ulcer), type 3 (prepyloric ulcer), type 4 (juxtacardia ulcer), and type 5 (greater curvature ulcer). Similar to duodenal ulceration, *H pylori* infection plays an important role in the pathogenesis of benign gastric ulcers. Antibiotic *Helicobacter* treatment regimens useful for duodenal ulcer have also been used for benign gastric ulceration. The response of gastric ulcers to *Helicobacter* treatment is equivalent to that of duodenal ulcers. Recurrence or persistence of gastric ulcers after *H pylori* eradication may indicate persistent or recurrent infection, but more likely represents persistence of other risk factors such as smoking and/or NSAID use. In addition to *H pylori* infection, alterations in gastric motility have been demonstrated in some patients with benign gastric ulcers. Motility defects include delayed gastric emptying, abnormal pyloric sphincter function, prolonged high-amplitude gastric contractions, duodenogastric reflux, and alterations in the gastric migrating motor complex. These alterations have not been definitively demonstrated to be pathogenic, and their relevance to gastric ulceration is unsettled.

Marginal ulcers are peptic ulcers which characteristically occur on the jejunal side of the gastrojejunostomy following distal gastrectomy, gastric bypass, or simple gastrojejunostomy. The risk of marginal ulceration is related to the acid/peptic load delivered into the jejunum (a site unaccustomed to any acid), and luminal jejunal buffering (largely absent in Roux gastrojejunostomy). So risk factors for marginal ulceration include Roux gastrojejunostomy, large gastric pouch after distal gastrectomy or Roux-en-Y gastric bypass (RYGBP), gastrogastric fistula after RYGBP, retained or excluded antrum, and incomplete or inadequate vagotomy. Other factors to consider are ischemia and permanent suture material. Marginal
Ulcers are prone to the same complications that bedevil duodenal or gastric ulcer including perforation, obstruction, bleeding, and nonhealing. Cancer is usually not a concern with marginal ulcer unless the anastomosis was performed many years ago, and then stump cancer becomes a consideration.

**Operative Treatment of Peptic Ulcer Disease**

It is well recognized that elective operation for intractable peptic ulcer disease has largely disappeared. Operative intervention is now performed primarily for the treatment of ulcer complications which are (in decreasing order of operative frequency): perforation, obstruction, bleeding, and nonhealing (*Table 29-5*). The role of the traditionally “definitive” ulcer operations (parietal cell vagotomy, vagotomy and drainage, vagotomy and antrectomy) is less clear. Both surgeon questionnaire and evaluation of administrative database suggest that vagotomy for ulcer nowadays is unusual, as is definitive ulcer operation in the setting of perforation or bleeding. Cancer remains an important part of the differential diagnosis in gastric ulcer, obstructing peptic ulcer disease, and marginal ulcer if (it occurs many years after gastrojejunostomy). Ultimately, recurrent peptic ulcer is almost inevitable if one or more of the following persist: *Helicobacter* infection, NSAID use, smoking, inadequate acid suppression. Lifelong acid suppression should be considered in all patients hospitalized for peptic ulcer. The operative mortality for emergency ulcer operation is 10% to 20%. This speaks to the frailty and degree of chronic illness seen in many patients requiring peptic ulcer surgery today.

**TABLE 29-5: SURGICAL OPTIONS FOR PEPTIC ULCER**
Perforated Peptic Ulcer

Patients with perforated peptic ulcer have a hospital mortality risk of 10% to 20%. Most patients with perforated peptic ulcer are adequately treated by peritoneal washout and omental patch, with subsequent elimination of risk factors (ie, treat *Helicobacter*; stop smoking; stop NSAIDs; take acid suppression). The postoperative elimination of risk factors is very important. In the absence of peritonitis and systemic inflammatory response, nonoperative management may be considered if careful radiologic evaluation confirms that the ulcer has sealed. However, the large majority of patients with perforated ulcer need urgent operation, which can be done laparoscopically or open. Biopsy to rule out cancer should be done in patients with perforated gastric ulcer, and perforated marginal ulcer if the gastrojejunostomy was done many years ago. Wedge resection may be preferable to omental patch for some perforated gastric ulcers. In the setting of shock, perforation >48 hours, or dangerous medical comorbidity (eg, recent MI, pulmonary hypertension, multisystem organ failure [MSOF], cirrhosis), definitive ulcer operation should be eschewed. In the stable patient, definitive operation may be considered for chronic ulcer which has failed medical management and if postoperative elimination of risk factors is unlikely.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duodenal</th>
<th>Gastric</th>
<th>Marginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation</td>
<td>Patch</td>
<td>Biopsy and patch</td>
<td>Patcha</td>
</tr>
<tr>
<td></td>
<td>Patch+HSV</td>
<td>Excise ulcer/close defectc</td>
<td>Resection of GJ</td>
</tr>
<tr>
<td></td>
<td>Patch+TV/D</td>
<td>Distal gastrectomy w ulcer</td>
<td>Resection of GJ</td>
</tr>
<tr>
<td></td>
<td>TV+A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Oversew alone</td>
<td>Biopsy and oversew</td>
<td>Oversew aloneb</td>
</tr>
<tr>
<td></td>
<td>Oversew+TV/D</td>
<td>Distal gastrectomy w ulcer</td>
<td>Resection of GJ</td>
</tr>
<tr>
<td></td>
<td>TV+A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>HSV+GJ</td>
<td>HSV+GJ/ulcer biopsy</td>
<td>Resection of GJ</td>
</tr>
<tr>
<td></td>
<td>TV+GJ</td>
<td>TV+GJ/ulcer biopsy</td>
<td>Resection of GJ</td>
</tr>
<tr>
<td></td>
<td>TV+A</td>
<td>TV+A</td>
<td></td>
</tr>
<tr>
<td>Nonhealing‡</td>
<td>HSV+GJ</td>
<td>Wedge resection</td>
<td>Resection of GJ</td>
</tr>
<tr>
<td></td>
<td>TV+A‡</td>
<td>Distal gastrectomyd</td>
<td></td>
</tr>
</tbody>
</table>

aUnless excised, gastric ulcers should be biopsied.

bIf GJ done many years ago, biopsy should be considered.

cDepends on location of ulcer.

dWhenever possible, operation should be delayed until smoking and NSAIDs are eliminated. Autonomic hypergastrinemia secondary to gastrinoma or retained antrum should be ruled out.

‡Historically, distal gastric resection has been the operation of choice for nonhealing duodenal or gastric ulcer. This operation should be avoided in thin patients, particularly in those who continue to smoke and/or take NSAIDs.
Though simple omental patch with postoperative Helicobacter treatment has been shown to eliminate recurrent or persistent ulcer symptoms in most patients with perforated duodenal ulcer, some patients will fail H pylori eradication or have other significant risk factors such as smoking and NSAID use. Furthermore, extrapolation from duodenal ulcer to gastric or marginal ulcer may be inappropriate. Thus it is reasonable to consider definitive operation on a case-by-case basis in the stable patient with peptic ulcer perforation. For perforated duodenal ulcer, definitive procedures include parietal cell vagotomy, truncal vagotomy and drainage (pyloroplasty incorporating the perforation or gastrojejunostomy), and truncal vagotomy and antrectomy (perhaps most appropriate for giant duodenal perforations). For perforated gastric ulcer, definitive operations include distal gastrectomy to include the ulcer, and wedge resection with vagotomy and drainage. For marginal ulcer, definitive operation includes resection of the gastrojejunostomy with the perforation, along with additional stomach if deemed appropriate.

**Obstructing Peptic Ulcer**

By far the most common cause of gastric outlet obstruction is cancer (pancreas, duodenum, stomach), and it is worthwhile keeping this in mind when treating patients for peptic ulcer obstruction. All three peptic ulcer varieties (duodenal, gastric, marginal) can cause chronic scarring resulting in intractable gastric outlet obstruction manifested by chronic nausea, vomiting, epigastric pain, weight loss, food intolerance, and even sitophobia. Patients with suspected obstructing peptic ulcer should have upper endoscopy with biopsy and CT scan. Traditional barium fluoroscopic studies may also be revealing. Endoscopic balloon dilation can be transiently helpful in up to half of these patients, but multiple dilations are usually necessary and most patients eventually require operation. The gold standard procedure for obstructing duodenal or prepyloric gastric ulcer is distal gastrectomy with Billroth 2 gastrojejunostomy, and truncal vagotomy. An acceptable alternative operation is laparoscopic gastrojejunostomy and selective vagotomy, which can be done minimally invasively. If the obstructing ulcer disease is primarily prepyloric, attempt should be made to obtain lumenal biopsies at the site of obstruction. Subsequently, if indicated, the gastrojejunostomy can be reversed (eg, for severe dumping if the pyloric
channel is patent) or converted to distal gastrectomy with Billroth 2 or Roux gastrojejunostomy (eg, for persistent symptoms or concern about malignancy). However, this “lesser operation” may miss or delay the diagnosis of an unexpected obstructing cancer. The hospital mortality for patients with obstructing peptic ulcer is 2% to 3%.

**Bleeding Peptic Ulcer**

Although bleeding remains the most common reason for hospitalization in peptic ulcer patients, with a hospital mortality around 3%, it is no longer a common indication for surgery due to the efficacy of endoscopic treatment and occasionally radiologic embolization. Aggressive treatment with IV acid suppression is important too. Bleeding peptic ulcer is the most common cause of clinically significant upper GI bleeding. Most patients (75%) have low-risk bleeds, but 25% of patients have high-risk bleeds, and essentially all the deaths from bleeding ulcer occur in this latter group. Clinical and endoscopic parameters can identify this high-risk group (Table 29-6), which should be managed by a multidisciplinary team in a special unit or intensive care unit. After initial resuscitation, early endoscopy should be performed and bleeding sites treated with epinephrine injection and an energy source. Endotracheal intubation for airway protection is considered on a case-by-case basis. Rebleeding should prompt repeat endoscopic treatment or angiography. Surgery should be considered for refractory bleeding requiring multiple transfusions, especially if associated with episodes of hemodynamic instability, and for high-risk lesions, such as deep penetrating ulcer with a subjacent named artery. Bleeding from erosion of the ulcer into the gastroduodenal, left gastric, or splenic artery is very likely to persist or recur after endoscopic therapy alone.

**TABLE 29-6: ULCER STIGMATA AND REBLEEDING IN PEPTIC ULCERS**
Bleeding marginal ulcers are best treated with resection. Occasionally the ulcer has eroded into named vessels such as the splenic artery or middle colic artery, so the surgeon should be prepared for these contingencies. Bleeding gastric ulcer can be treated with oversewing, wedge resection, or definitive gastrectomy to include the ulcer. Traditionally, vagotomy for gastric ulcer has been deemed unnecessary. Though hemigastrectomy and damage control remains an option, it is best to avoid definitive ulcer operation in the setting of shock or profound coagulopathy. Surgical options for the management of bleeding duodenal ulcer include oversewing, either alone or with definitive ulcer operation, usually vagotomy and drainage. Classically the pyloroduodenotomy, which is made to access the bleeding ulcer, is incorporated into a pyloroplasty. Alternatively, the pyloric incision is closed and gastrojejunostomy performed. Then truncal vagotomy is done. Antrectomy with truncal vagotomy can be considered in stable patients, especially those with giant bleeding duodenal ulcer. However, management of the duodenal stump can be challenging since the ulcer must be securely oversewn or resected.

Regardless of operation performed, certain and secure ulcer hemostasis by suture ligation should be the most important goal of any operation for bleeding peptic ulcer. Much has been written about the proverbial and useful “U-stitch” to secure hemostasis in a deep duodenal ulcer with a hole in the gastroduodenal artery near a large pancreatic side branch. Deep “over-and-over” sutures may accomplish the same thing. Extralumenal ligation of the gastroduodenal or left gastric artery may occasionally also be helpful. Compared to simple oversewing and vagotomy and drainage, rebleeding may

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>Rebleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active arterial bleeding</td>
<td>12</td>
</tr>
<tr>
<td>Nonbleeding visible vessel</td>
<td>22</td>
</tr>
<tr>
<td>Nonbleeding flat clot</td>
<td>10</td>
</tr>
<tr>
<td>Oozing</td>
<td>14</td>
</tr>
<tr>
<td>Nonbleeding flat spots</td>
<td>10</td>
</tr>
<tr>
<td>Clean ulcer base</td>
<td>32</td>
</tr>
</tbody>
</table>

be less common after distal gastrectomy for bleeding peptic ulcer, but the operative mortality is higher. Overall, current hospital mortality in patients requiring operation for bleeding peptic ulcer is 10% to 20%.

**Intractable or Nonhealing Peptic Ulcer**

Operation for nonhealing peptic ulcer should be performed only after careful deliberation and diagnostic evaluation. Nonhealing or intractability should indeed be a rare indication for ulcer operation today, and the patient referred for surgical evaluation of intractable peptic ulcer disease should raise red flags for the surgeon. Since acid secretion can be totally blocked and *H pylori* eradicated with modern medication, it is important to ask why the patient has a persistent ulcer diathesis. All causes of nonhealing peptic ulcer should be considered prior to operative treatment (Table 29-7).

<table>
<thead>
<tr>
<th>TABLE 29-7: DIFFERENTIAL DIAGNOSIS OF INTRACTABILITY OR NONHEALING PEPTIC ULCER DISEASE</th>
</tr>
</thead>
</table>
| **Cancer**  
| - Gastric  
| - Pancreatic  
| - Duodenal  
| **Persistent *H pylori* infection**  
| - Tests may be false negative  
| - Consider empiric treatment  
| **Noncompliant patient**  
| - Failure to take prescribed medication  
| - Surreptitious use of nonsteroidal anti-inflammatory drugs  
| **Motility disorder**  
| **Zollinger-Ellison syndrome**  
| **Ischemia**  |


Surgical treatment may be considered in patients with nonhealing or intractable peptic ulcer disease who have multiple recurrences, large ulcers...
(>2 cm), complications (obstruction, perforation, or hemorrhage), or suspected gastric cancer. Though nonhealing ulcers may represent an undiagnosed malignancy, this is unusual nowadays. Typically patients with intractable or nonhealing peptic ulcer experience suboptimal outcomes after ulcer operation, which may result in chronic weight loss of up to 10% to 20%. Before embarking on an ulcer operation in a patient for intractability or nonhealing, it is prudent for the surgeon to envision this degree of weight loss, since this is what the patient might look like after an ill-conceived ulcer operation. The obvious corollary is that operation for intractability or nonhealing ulcer should be avoided in asthenic patients. Sadly, the thin patient can be an easy target for a big ulcer operation in the hands of the inexperienced ulcer surgeon.

Prior to operation for intractable or nonhealing peptic ulcer, empiric *Helicobacter* treatment should be administered; smoking and NSAIDs should be stopped. Patient, family, surgeon, and gastroenterologist should understand the risks and likely outcomes of operation. It is important to realize that operative results for ulcer intractability today will not mirror those obtained 40 to 50 years ago, since the surgical populations are different. Formal distal gastric resection should be avoided if possible. For intractable duodenal ulcer, consideration should be given to parietal cell vagotomy, with or without gastrojejunostomy, which is reversible. For intractable or nonhealing gastric ulcer, wedge excision with or without parietal cell vagotomy should be considered as an alternative to distal gastrectomy when technically feasible.

It is important that the surgeon not fall into the trap of performing a large, irreversible operation on these patients based on the unproven theory that if all other methods have failed, a larger operation is required. Today’s patients are different than those of three or four decades ago. One might argue that modern medical care has healed the minor ulcer, and that patients presenting with true intractability or nonhealing will be more difficult to treat and are likely to have chronic problems after a major ulcer operation. If surgery is necessary, less is often better. It is the practice of the authors never to perform a gastrectomy as the initial elective operation for intractable duodenal ulcer in the thin or asthenic patient. Instead, the preferred operation for this group of patients is HSV. In patients with nonhealing gastric ulcer, wedge resection with HSV should be considered in thin or frail patients. Otherwise distal gastrectomy (to include the ulcer) is recommended. It is
unnecessary to add a vagotomy in patients with type I gastric ulcer.

**Technical and Physiological Considerations**

Transection of both vagal trunks at the esophageal hiatus, termed truncal vagotomy, severs vagal input to the abdominal viscera. Truncal vagotomy eliminates the cephalic phase of gastric acid secretion and alters antral and pyloric motor function, often (but not always) resulting in delayed gastric emptying. Thus, truncal vagotomy is usually combined with a procedure to eliminate or bypass pyloric sphincter function, for example pyloroplasty or gastrojejunostomy. Several methods of pyloroplasty have been developed. The Heineke–Mikulicz pyloroplasty (Fig. 29-2) consists of a longitudinal incision of the pyloric sphincter extending into the antrum and the duodenum. The incision is closed transversely, eliminating sphincteric closure and increasing the lumen of the pyloric channel. The Finney pyloroplasty (Fig. 29-3) extends the pyloric incision 5 cm onto the duodenal wall, forming an inverted U-shaped incision after the placement of superior and inferior traction sutures. Once traction is applied, the two limbs of the inverted U-shaped incision are lined up and sutured to each other to complete the procedure, with the inferior suture line forming the posterior wall and the superior suture line forming the anterior wall of the pyloroplasty. A Jaboulay gastroduodenostomy (Fig. 29-4) requires more extensive dissection, beginning with a Kocher maneuver followed by corresponding incisions on the stomach and the duodenum proximal and distal to the pylorus, respectively. Traction sutures are then placed between the stomach and duodenum to approximate the two incisions, and the anastomosis is then performed.

Truncal vagotomy can be combined with resection of the gastric antrum to further reduce acid secretion by removing antral sources of gastrin. The limits of antral resection are defined by external landmarks. The stomach is divided proximally along a line from a point above the incisura angularis on the lesser curvature to a point somewhere along the greater curvature midway between the pylorus and the inferior tip of the spleen. Reconstruction via a gastroduodenostomy is called a Billroth I procedure. A Billroth II procedure
uses a gastrojejunostomy to restore GI continuity.

Proximal gastric vagotomy, also termed highly selective vagotomy (HSV), differs from truncal vagotomy in that only the nerve fibers to the acid-secreting fundic mucosa are transected (Fig. 29-5). The hepatic and celiac divisions are not divided, and vagal nerve fibers to the antrum and pylorus remain intact. The operation has also been called parietal cell vagotomy to emphasize the intended functional consequence. Proximal gastric vagotomy is a safe operation with an elective operative mortality rate of less than 0.1% in a good risk patient. Truncal vagotomy and pyloroplasty has an accepted mortality rate of 0.5% to 0.8%, whereas operative mortality after truncal vagotomy and antrectomy approximates 1.5%. Note that these statistics, acquired decades ago, represent the results of elective operations on mostly good risk patients with peptic ulceration and may not accurately reflect expected results when similar procedures are performed urgently in patients with multiple comorbidities.
Division of vagal nerve fibers alters gastric acid secretion by reducing cholinergic stimulation of parietal cells. Vagal denervation also decreases parietal cell responsiveness to gastrin and histamine. Basal acid secretion is diminished by approximately 80% in the immediate postoperative period and
is maintained over time. The maximal acid output in response to secretagogues such as pentagastrin is reduced by approximately 70%. After 1 year, pentagastrin-stimulated maximal acid output increases to 50% of pre-vagotomy values but remains at this level on subsequent testing. Acid secretion due to meal stimulation is reduced by 60% to 70% relative to normal subjects. The inclusion of antrectomy to truncal vagotomy further reduces acid secretion. Maximal acid output is reduced by 85% relative to values recorded before antrectomy.

Operations that involve vagotomy affect gastric emptying. Both truncal vagotomy and proximal gastric denervation abolish vagally mediated receptive relaxation that normally allows the ingestion of a meal with no increase in intragastric pressure. After vagotomy, the intragastric pressure rise is greater for any given volume ingested, and the gastroduodenal pressure gradient is higher than in normal subjects. As a result, emptying of liquids, which depends on the gastroduodenal pressure gradient, is accelerated. Because nerve fibers to the antrum and pylorus are preserved with proximal gastric vagotomy, the function of the distal stomach to mix solid food is preserved, and emptying of solids is nearly normal. Truncal vagotomy affects the motor activity of the distal stomach, and solid and liquid emptying rates are usually increased when truncal vagotomy is accompanied by pyloroplasty.

Though uncommonly performed today, gastric ulcer in the good risk well-nourished patient is perhaps best treated with distal gastrectomy (including the ulcer in the specimen) (Fig. 29-6) with either gastro-duodenal (Billroth I) or gastrojejunal (Billroth II) anastomosis. Performed electively, operative mortality approximates 2% to 3%, and ulcer recurrence rates are less than 5%. Unlike antrectomy for duodenal ulcer, inclusion of vagotomy does not decrease recurrence rates for gastric ulcer, which is not surprising given the variability of acid secretion in patients with gastric ulcers. The occurrence of a benign ulcer near the gastroesophageal junction (type IV ulcer) represents a difficult surgical problem. The ulcer may be excised via a distal gastrectomy with an extension along the lesser curvature into the cardia and reconstruction with Roux gastrojejunostomy (Csendes operation). Alternative procedures to deal with proximal gastric ulcers include the Pauchet gastrectomy and the Kelling-Madlener procedure (Fig. 29-7). Type V gastric ulcers occur along the greater curvature and are best treated with wedge resection.
FIGURE 29-6 Points of transection for distal gastrectomy performed to resect a gastric ulcer along the lesser curvature. d, the approximate diameter of the duodenum.
POSTGASTRECTOMY SYNDROMES

Perhaps up to 30% of patients who have had operations on the stomach have some chronic symptoms, commonly referred to as “postgastrectomy syndromes.” However, the occurrence of permanent disabling postgastrectomy syndromes is uncommon (5% or less) and usually unpredictable. Symptoms typically include one or more of the following: diarrhea, vomiting, abdominal pain, and malnutrition or nutritional deficiency. These patients have had operations on the stomach for peptic ulcer, cancer, obesity, or gastroesophageal reflux disease (GERD). The frequency with which post-gastrectomy symptoms and syndromes are found
depends on how hard they are looked for. The incidence is high early postoperatively, but most patients report improvement within 1 year after surgery. The management of patients with these symptoms can be challenging but appropriate therapy can have a significant impact on the patient’s long-term outcome.

**Dumping Syndrome**

Dumping syndrome (DS) is a constellation of gastrointestinal and vasomotor symptoms that present postprandially due to rapid gastric emptying. It is caused by loss of pyloric regulation of gastric emptying and/or decreased gastric compliance. Early dumping symptoms occur within 1 hour of ingestion of a meal and include nausea, epigastric discomfort, tremulousness, and sometimes dizziness or syncope. Late dumping symptoms follow a meal by 1 to 3 hours. Late symptoms are usually due to reactive hypoglycemia.

The human stomach has the capability of adapting to large volumes of orally administered liquids and solids through vagally mediated accommodation and receptive relaxation. Procedures that alter the normal intragastric pressure/volume relationship (proximal gastric vagotomy, sleeve gastrectomy, fundoplication) or outflow resistance (pyloroplasty, gastrojejunostomy) predispose to DS. Procedures that alter both have the highest incidence of dumping (eg, distal gastrectomy, gastric bypass). Dumping symptoms have been reported in up to 70% of Billroth II patients and up to 75% of patients after RYGBP for obesity. Similarly, after gastrectomy for cancer, 67% of patients present with early dumping symptoms and 38% with late dumping. The role of surgically induced microbiome changes in the etiology of DS is unknown.

Early dumping is more common and includes systemic and abdominal symptoms. Systemic manifestations include palpitations, tachycardia, fatigue, a need to lie down following meals, flushing or pallor, diaphoresis, lightheadedness, hypotension, headache, and possibly syncope. Abdominal symptoms include early satiety, epigastric fullness or pain, diarrhea, nausea, cramps, bloating, and borborygmi. Early dumping begins within 30 min following a meal and is attributable to bowel distention, relative hypovolemia, gastrointestinal hormone hypersecretion, and autonomic dysregulation. Late dumping is characterized by symptoms that occur 1 to 3 h postprandial. Symptoms of late dumping consist of perspiration, faintness,
decreased concentration, and altered levels of consciousness, among others. These symptoms are related to a reactive hypoglycemia that occurs 1 to 3 h postprandial. Patients with late dumping often have early dumping as well. Most patients with DS have mild to moderate symptoms, but some patients have disabling symptoms that may be severe enough to cause protein–energy malnutrition.

An oral glucose challenge will confirm the diagnosis of DS. The diagnosis can also be made with a scintigraphic gastric emptying study, in which greater than 50% of an isotope-labeled solid meal has emptied within 1 hour. Early dumping tends to improve with time, whereas late dumping tends to persist or exacerbate.

In most patients with DS, symptoms are not severe and medical management is successful. Dietary modification such as frequent small meals and separating liquids and solids are the first line of treatment. Diets should be high in protein and fiber. Fat, milk, and simple sugars should be avoided.

A number of pharmacologic options exist for the treatment of DS. Octreotide, a somatostatin analogue, should be considered for patients with severe postgastrectomy DS refractory to diet therapy (Table 29-8). Octreotide can markedly improve the quality of life in DS patients. Long-term octreotide therapy may lose efficacy over time, as side effects, such as diarrhea and steatorrhea, and cost lead to lack of compliance. Acarbose is an α-glycosidase hydrolase inhibitor that delays carbohydrate digestion and absorption and is efficient in the treatment of late dumping. Diazoxide is a potassium channel activator that inhibits the secretion of insulin. Thus, diazoxide has showed success in treating late dumping hypoglycemia and can be used when acarbose and lifestyle modifications are insufficient.

### TABLE 29-8: OCTREOTIDE IN DUMPING SYNDROME

<table>
<thead>
<tr>
<th>Effect</th>
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<tr>
<td>Delay in the accelerated gastric emptying</td>
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<tr>
<td>Delay in small intestine transit time</td>
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<tr>
<td>Inhibition of enteral hormone secretion</td>
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<tr>
<td>Inhibition of insulin release</td>
</tr>
<tr>
<td>Inhibition of postprandial vasodilation/splanchnic vasoconstriction</td>
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<tr>
<td>Increase in intestinal absorption of water and sodium</td>
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Most patients improve with time (months and even years), dietary management, and medication. Therefore, the surgeon should not rush to reoperate on the patient with DS. Only a small percentage of patients with dumping symptoms ultimately require surgery. The results of remedial operation for dumping are variable and unpredictable. A variety of surgical approaches exist, none of which work consistently well. In addition, there is not a great deal of experience reported in the literature with any of these methods and long-term follow-up is rare. Patients with disabling refractory dumping after gastrojejunostomy can be considered for simple takedown of this anastomosis provided that the pyloric channel is patent endoscopically. For dumping following pyloroplasty, distal gastrectomy with Roux reconstruction is an option. For severe dumping after BI or BII gastrectomy, conversion to Roux-en-Y gastrojejunostomy may be considered, since dysmotility of the Roux limb tends to slow gastric emptying. In the presence of a sizable (>40%) gastric pouch with intact vagal innervation, lifelong acid suppression may be prudent in the setting of Roux gastrojejunostomy.

**Postvagotomy Diarrhea**

Truncal vagotomy is initially associated with clinically significant diarrhea in 5% to 10% of patients, but symptoms improve with time. The incidence of long-lasting postvagotomy diarrhea is 1% to 2%. The cause of postvagotomy diarrhea is unclear. Contributing factors include intestinal dysmotility with accelerated small bowel transit, bile acid malabsorption, rapid gastric emptying, altered microbiome, and bacterial overgrowth. Some patients with postvagotomy diarrhea respond to cholestyramine, while for others codeine or loperamide may be useful. In the rare patient who is debilitated by postvagotomy diarrhea unresponsive to maximal medical management for at least 1 year, surgery might be considered, but outcomes can be problematic. The 10-cm reversed jejunal interposition placed in continuity 100 cm distal to the ligament of Treitz has been described but can cause obstructive symptoms and/or bacterial overgrowth.

**Gastric Stasis**
In the rare patient with acute gastric stasis after gastric surgery, persistent nausea and vomiting prevent removal of the nasogastric tube in the absence of mechanical obstruction. If the symptoms persist beyond a period of 7 to 10 days after surgery, a gastrostomy can be placed and a J tube should be considered for enteral nutrition. In patients who are not candidates for enteral nutrition, total parenteral nutrition is an alternative. Reoperation should generally be delayed for at least 3 months, as the majority of patients will regain satisfactory GI function without surgery.

Chronic gastric stasis following gastric surgery may be due to a problem with gastric motor function or caused by an obstruction. Chronic gastric stasis presents with vomiting (often of undigested food), bloating, epigastric pain, and weight loss. Symptoms are usually improved by a liquid diet, and always improved by prolonged fasting. The evaluation includes EGD, upper GI series, gastric emptying scan (scintigraphy), and gastric motor testing. Endoscopy shows gastritis and retained food or bezoar in the stomach. The gastroenteric anastomosis and efferent limb should be evaluated for stricture or narrowing. A dilated efferent limb suggests chronic stasis, either from a motor abnormality (eg, Roux syndrome) or mechanical small bowel obstruction (eg, chronic adhesion). If the problem is thought to be primarily a disorder of intrinsic motor function, newer diagnostic techniques such as electrogastrography and GI manometry should be considered.

Once mechanical obstruction has been ruled out, medical treatment is successful in most patients. Management consists of dietary modification and promotility agents such as metoclopramide, domperidone, and erythromycin. Intermittent oral antibiotic therapy may be helpful in treating bacterial overgrowth. Probiotics should be tried, since alterations in gut microbiome are likely. Operation is reasonable when chronic postoperative gastric stasis is severe and resistant to medical management. At operation, small bowel obstruction and efferent limb obstruction should always be ruled out. Gastroparesis following vagotomy and drainage procedures may be treated with subtotal (75%) gastrectomy. Billroth II anastomosis with Braun enteroenterostomy may be preferable to Roux-en-Y reconstruction after subtotal gastrectomy in this setting, since Roux reconstruction may result in persistent gastric emptying problems (Roux syndrome). Gastroparesis following subtotal gastric resection is best treated with near-total (95%) or total gastric resection and Roux-en-Y reconstruction. High-frequency gastric electrical stimulation (GES) may be an effective treatment for patients with
postsurgical gastroparesis who failed standard medical therapy, but long-term data are lacking.

**Afferent and Efferent Loop Obstruction**

Afferent loop obstruction is a mechanical complication that typically occurs after Billroth II or loop gastrojejunostomy. Etiologies include (1) entrapment, compression, and kinking of the afferent loop by postoperative adhesions; (2) internal herniation, volvulus, and intussusception of the afferent loop; (3) scarring due to marginal ulceration of the gastrojejunostomy; (4) locoregional recurrence of cancer (lymph nodes, peritoneum, gastric remnant, anastomotic sites); (5) radiation enteritis of the afferent loop; and (6) enteroliths, bezoars, and foreign bodies impacted in the afferent loop. Although both acute and chronic forms of afferent loop syndrome have been described, chronic partial obstruction is the more common clinical manifestation. The classic presentation of chronic afferent loop syndrome is postprandial abdominal pain relieved by bilious vomiting. A meal elicits pancreatic, biliary, and duodenal secretion into the obstructed afferent limb. Eventually the pressure in the partially obstructed afferent limb overcomes the obstruction (usually 30-60 minutes postprandial), delivering a large volume of bilious secretions into the stomach or Roux limb. This leads to bilious vomiting and prompt relief of the pain, which was caused by the afferent limb distention. Obstruction of the biliopancreatic limb following RYGBP must also be considered an afferent loop obstruction and typically presents with postprandial abdominal pain; bilious vomiting is usually lacking because of the long Roux limb.

If the obstruction is high grade or complete, the distended afferent loop may not sufficiently decompress, leading to acute afferent loop obstruction. In this scenario, vomiting, if present, will be nonbilious, and a clinical picture of “closed loop obstruction” manifested as an acute abdomen will result. If this condition is not recognized early, the afferent loop may actually perforate and result in peritonitis. Urgent intervention or surgery is necessary to correct this problem. Abdominal CT is the diagnostic study of choice. CT appearance of the obstructed afferent loop consists of a C-shaped, fluid-filled tubular mass located in the midline between the abdominal aorta and the superior mesenteric artery (c-loop sign) with valvulae conniventes projecting into the lumen (keyboard sign).
Although endoscopic interventions and/or percutaneous approaches may be useful in special cases (eg, carcinomatosis or extremely high operative risk), the cornerstone of treatment for afferent loop obstruction is operation. In contrast to the relatively stereotypical manifestation of afferent loop obstruction, efferent loop obstruction generally mimics proximal small bowel obstruction. It is most commonly caused by adhesions, but internal hernia must also be considered.

**Alkaline (Bile) Reflux Gastritis**

Alkaline reflux gastritis is presumably caused by the longstanding presence of an abnormal amount of duodenal content in the stomach or gastric remnant, a situation that often occurs in patients after pyloroplasty or loop gastrojejunostomy with or without gastric resection. A distinction must be made between histologic bile gastritis, which is present in many patients after gastric surgery (up to 85% in Billroth II patients), most of whom are asymptomatic, and the presence of clinical bile gastritis leading to significant symptoms, a much more unusual situation. Gastric stasis may potentiate the damaging effects of duodenal contents on the gastric mucosa. Smoking and NSAIDs also may contribute. In a subset of patients, bile gastritis leads to metaplasia and dysplasia, and some of these patients progress to gastric cancer (“stump cancer”). Many patients have histologic gastritis after gastric surgery, but clinically significant bile reflux gastritis is not common and the relationship of chronic gastric mucosal inflammation to symptoms in this setting is not well defined. The most common symptoms attributed to chronic bile gastritis are abdominal pain and bilious vomiting. The pain is typically not relieved by antacids or acid suppressive medication. Unlike afferent limb syndrome, the pain does not resolve after vomiting.

The diagnosis of alkaline reflux gastritis is essentially a diagnosis of exclusion and is largely based on symptomatology. The first step in patient evaluation is endoscopy. Inflammatory changes in the stomach involving more than just the peristomal area are supportive, but not specific for bile reflux. Mucosal biopsies will show the characteristic histologic features of bile reflux. However, the endoscopic and histological features of bile gastritis are frequently observed in asymptomatic patients, and the extent of the findings does not correlate well with the severity of symptoms. Hepatobiliary iminodiacetic acid (HIDA) scans can provide a semiquantitative assessment
of bile reflux/stasis in the stomach. Upper gastrointestinal barium study, ultrasound, and CT scan may also be useful.

Medical management includes cholestyramine, antacids, H2 blockers, proton pump inhibitors, sucralfate, or promotility agents to enhance clearance of refluxate from the gastric remnant. When these measures fail, surgery is considered for patients with incapacitating symptoms, a reasonably secure clinical diagnosis, and realistic expectations. Preoperative nutritional support may be required and jejunostomy tube placement should be considered strongly during remedial operation, the aim of which is diversion of duodenal contents away from the stomach.

The Roux-en-Y gastrojejunostomy is the surgical reconstruction most frequently chosen to treat patients with alkaline reflux gastritis (Fig. 29-8). Conversion of BI or BII to Roux-en-Y gastrojejunostomy with a 60-cm Roux limb reliably diverts intestinal contents from the gastric remnant and improves symptoms in up to 85% of patients. This procedure also results in significant improvement of endoscopic findings. Although Roux-en-Y gastrojejunostomy achieves satisfactory symptom relief following surgery, during long-term follow-up epigastric pain may persist, particularly in those patients using narcotics preoperatively. The only symptom that is consistently relieved is bilious vomiting, but some patients develop worsening delayed gastric emptying. Other surgical options for postoperative bile gastritis include Braun enteroenterostomy between the afferent and efferent limbs of BII or loop gastrojejunostomy, Henley isoperistaltic jejunal interposition between stomach and duodenum, and duodenal switch. The latter was described to treat primary bile reflux gastritis, which occurs rarely, and absent any previous operation of the stomach or duodenum, but it might be a reasonable surgical option in the rare patient who has acquired debilitating bile reflux gastritis after pyloroplasty or B-I gastroduodenostomy.
Roux-en-Y gastrojejunostomy used to treat alkaline reflux gastritis. (Reproduced with permission from Schwartz SI, Ellis H: Maingot’s Abdominal Operations, 9th ed. Stamford, CT: Appleton & Lange; 1989.)

**Roux Stasis Syndrome**

After distal gastrectomy with Roux-en-Y reconstruction, some patients experience symptomatic delayed gastric emptying of solids. This phenomenon has been termed the “Roux stasis syndrome” since it has generally been attributed to measurable abnormalities in Roux limb motility.
Of note, Roux syndrome is more common in the presence of a large gastric remnant or after vagotomy, and quite uncommon after Roux-en-Y gastric bypass.

Symptoms of Roux syndrome include abdominal pain and distention, postprandial bloating, nausea, and vomiting. Typically the vomitus contains solid food and is nonbilious. Bacterial overgrowth, with diarrhea and nutrient malabsorption, may result. Endoscopically, the gastric remnant may be dilated with retained food and mucosal irritation. The anastomosis is patent and the Roux limb may also be dilated. There is no evidence of mechanical obstruction on CT or upper GI series. Scintigraphy shows markedly delayed emptying of solids. Liquid emptying is usually not delayed.

Most patients with the Roux syndrome can be successfully managed conservatively with dietary manipulations and use of prokinetic agents, but some patients require revisional operation in an attempt to relieve debilitating symptoms and improve nutritional status. In general, the operation of choice is near-total or total gastrectomy with anastomosis to a new Roux limb (usually the original Roux should be resected). The addition of a feeding jejunostomy is prudent. Pacing of the intestine and/or stomach has been investigated as potential nonsurgical treatment, but this has not yet been proven effective as long-term treatment.

**Marginal Ulcers**

Marginal ulceration (ie, juxta-anastomotic ulceration) is a well-described complication of gastrojejunostomy and must be considered as part of the differential diagnosis for many of the more traditional post-gastrectomy syndromes. The incidence of marginal ulcer ranges from 0.6% to 25%. It is more common after Roux-en-Y anastomosis than after Billroth II because the former arrangement lacks the buffering afferent limb contents that counteract the noxious effect of gastric acid on the jejunal mucosa (usually the ulceration is on the jejunal side of the anastomosis). Chronic ischemia and permanent suture material may also be contributing factors. NSAIDs (including aspirin) and smoking predispose to marginal ulcer. Incomplete vagotomy, *Helicobacter* infection, and hypergastrinemia must also be considered. In most cases, marginal ulcers can be adequately treated with PPIs, the elimination of NSAIDs, *Helicobacter* treatment, and smoking cessation. Vagotomy and/or lifelong PPI therapy should also be considered.
Hypergastrinemia after distal gastrectomy can be caused by gastrinoma or retained antrum. In the latter there is residual antral tissue left in continuity with the duodenal stump after gastric resection with Billroth II anastomosis. A similar situation can be created inadvertently during revisional gastric bypass operation if the proximal bypassed stomach is resected and the distal bypasses stomach left in situ. Clinical suspicion of retained antrum may be confirmed by technetium 99 scan, and resection is curative. Gastrinoma is suspected when secretin infusion leads to significant further elevation of gastrin level. CT, endoscopic ultrasound (EUS), and octreotide scan may be helpful, but exploration by an experienced surgeon is the best way to find the tumor(s) if operation is indicated.

**Nutritional Abnormalities**

Weight loss is common in patients who have had a gastric operation for tumor or ulcer. The degree of weight loss tends to parallel the magnitude of the operation and should be considered as part of the preoperative decision making. Anemia is also a common finding in postgastrectomy patients, occurring in up to one-third of patients. This is generally secondary to nutrient malabsorption, but can also be caused by decreased nutrient intake or chronic blood loss due to ulcer, tumor, or mucosal inflammation. Iron, B<sub>12</sub>, and folate deficiencies are the most common cause of chronic nutritional anemia after gastric surgery. Chronic calcium deficit and osteoporosis may occur after gastric operation. Calcium absorption occurs primarily in the duodenum, so any gastric operation that diverts the food stream away from the duodenum will disturb calcium homeostasis. Finally, any gastric procedure that predisposes to bacterial overgrowth or inadequate mixing of food and digestive enzymes may interfere with the absorption of fat-soluble vitamins, including vitamin D. Thus, it is likely that both calcium and vitamin D malabsorption contribute to metabolic bone disease in patients following gastric surgery.

**STRESS ULCER DISEASE**

Gastritis and gastric ulceration can be induced by physiologic stress, which compromises mucosal defenses against acid peptic injury. Though some
acute stressors (eg, intracranial hypertension) may be surprisingly associated with increased gastric acid secretion, decreased gastric mucosal blood flow is a major factor in the development of “stress gastritis,” which has largely disappeared as an indication for operation owing to advances in critical care and probably also to stress ulcer prophylaxis. Usually occurring in hospitalized patients with critical illness (Table 29-9), stress gastritis can be demonstrated endoscopically in the majority of patients recovering from shock. While occult bleeding in this population is common, clinically significant hemorrhage defined by the need for blood transfusion, hypotension, or alteration in other vital signs occurs in only 0.5% to 5% of patients. In four recent surgical series comprising more than 28,000 patients, the incidence of clinically significant stress ulceration was 0.4%. In another series of 16,612 hospitalized patients, the incidence of overt stress bleeding was only 0.1%. In a review of patients admitted to both surgical and medical intensive care units (ICUs), the incidence of clinically significant and endoscopically proven stress ulceration was 0.17%.

TABLE 29-9: RISK FACTORS FOR STRESS ULCER BLEEDING

- Respiratory failure
- Coagulopathy
- Hypotension
- Sepsis
- Hepatic failure
- Renal failure
- Steroids
- Injury Severity Score >16
- Spinal cord injury
- Age >55 y

Major trauma (especially if accompanied by hypotension) sepsis, respiratory failure, hemorrhage, or multiple injuries predispose to acute stress gastritis. Acute stress gastritis is also common after thermal injury with greater than 35% total body surface area burned. A form of gastritis similar to that following trauma may complicate central nervous system (CNS) injury
or intracranial hypertension. When viewed endoscopically, multiple ulcerations are observed in the proximal, acid-secreting portion of the stomach. Fewer lesions are found in the antrum, and only rare ulcerations in the duodenum.

The major complication of stress gastritis is hemorrhage. Patients with coagulopathy and those requiring mechanical ventilation are at increased risk of hemorrhage. Patients without these two risk factors have been reported to have an overall risk of hemorrhage of only 0.1%, while those with both demonstrate clinically significant bleeding in 3.7% of cases. Respiratory failure is defined as greater than 48 hours on a mechanical ventilator. Coagulopathy is defined as a platelet count less than 50,000/μL, an international normalized ratio greater than 1.5, or a partial thromboplastin time greater than two times control.

Admission to an ICU does not by itself place patients at risk for hemorrhage, and patients undergoing major GI surgery do not have an increased risk of stress-related bleeding in the absence of complications. Increased patient age, emergency surgery, need for reoperation, and the occurrence of hypotension are risk factors for postoperative gastric bleeding. The occurrence of sepsis and respiratory failure are also risk factors. Multiple regression analysis has shown that mechanical ventilation and coagulopathy impart the greatest risk.

The diagnosis of stress ulceration requires endoscopic examination. Acute mucosal ulcerations may be observed as early as 12 hours post-insult—lesions appear as multiple shallow areas of erythema and friability, accompanied by focal hemorrhage. Histologically, the lesions consist of coagulation necrosis of the superficial surface epithelium with infiltration of leukocytes into the lamina propria. Signs of chronicity, such as fibrosis and scarring, are absent. With resolution of injury or sepsis, healing is accomplished by mucosal restitution and regeneration.

Stress ulcer prophylaxis is unnecessary in most elective surgery patients but should be considered in ICU patients with mechanical ventilation >48 hours, coagulopathy, burns, CNS injury, recent history of peptic ulcer or upper GI bleeding, and shock. Most commonly H2 blockers or PPIs are used; both enteral or parenteral routes of administration are acceptable. Suppression of gastric acid secretion has been implicated in the development of nosocomial pneumonia and Clostridium difficile infection, so indiscriminate or unnecessary use of these agents in hospitalized patients should be avoided.
A survey of Society of Critical Care Medicine members showed that ranitidine, famotidine, sucralfate, and cimetidine were the drugs used most commonly for prophylaxis. The presence of bright red blood in the nasogastric tube was considered by most to define prophylaxis failure, and the addition of a second drug from a different therapeutic class was the preferred mode of treatment. Because hemorrhage does not occur in all patients, studies that use bloody nasogastric discharge as a sign of stress gastritis underestimate the true incidence in critically ill patients. In one endoscopically controlled study, 100% of patients with life-threatening injuries had evidence of gastric erosions by 24 hours. A high prevalence of gastric erosions is also noted in burn patients, while GI hemorrhage occurs in only 25% to 50% of patients with burn wound infection. Barium contrast examinations have no role in the diagnosis of stress gastritis and interfere with endoscopic examination.

**GASTRIC EPITHELIAL POLYPS**

Gastric epithelial polyps (Table 29-10) are the most common benign tumors of the stomach, and they are usually found incidentally on EGD or upper GI. The two most common gastric polyps are fundic gland polyps and hyperplastic polyps. Both tend to be multiple.
Fundic gland polyps
Commonly seen in patients on chronic PPI; typically multiple, in proximal stomach
Biopsy for diagnosis
Total polypectomy if >1 cm, ulcerated, or antral location
Suspect polyposis syndrome if associated with gastroduodenal adenomas in young patient
High-grade dysplasia in fundic gland polyp possible w polyposis syndromes
Stop PPI if >20 fundic gland polyps or if fundic gland polyp >1 cm

Hyperplastic polyps
Occur in the setting of atrophic gastritis due to Helicobacter, autoimmune, bile reflux
Up to 20% have focus of dysplasia; 2% have cancer (mostly polyps >2 cm)
Remove all hyperplastic polyps >0.5 cm and repeat EGD in 6 months
Periodic surveillance EGD is prudent for extensive or advanced atrophic gastritis

Adenomatous polyps
Usually solitary, sessile, and distal in stomach
Associated with atrophic gastritis and gastric metaplasia/dysplasia
Definite cancer risk, both in polyp and remotely in stomach
All adenomatous polyps should be removed and remote gastric biopsies done
Endoscopic surveillance for all patients with adenomatous gastric polyp(s)

Fundic gland polyps are most commonly associated with chronic PPI use but they may occur as part of polyposis syndromes. They are thought to have very low malignant potential, but a substantial percentage of fundic gland polyps arising in patients with familial adenomatous polyposis (FAP) may show dysplasia. Progression to cancer is rare. Polyposis syndrome should be considered when numerous fundic gland polyps are encountered in young
patients and/or when concomitant distal gastric polyps or duodenal adenomas are found. Fundic gland polyps should be removed and PPIs stopped if the polyp(s) exceeds 1 cm in size or is ulcerated, or is distally located (we also stop PPIs for >20 fundic gland polyps). Otherwise, simple confirmatory biopsy is adequate. Routine endoscopic surveillance is unnecessary unless the patient has a polyposis syndrome or there is something unusual about the findings (large or distal polyps).

Hyperplastic polyps occur in the setting of chronic inflammation; eg, chronic gastritis or around a gastrojejunostomy. Up to 20% of hyperplastic polyps may have a focus of dysplasia, and larger polyps (>1 cm) or pedunculated lesions may contain cancer. Lesions >0.5 cm should be completely removed and the stomach should be assessed for metaplasia and dysplasia. *H pylori* should be eradicated, and follow-up endoscopy exam performed in about 6 months to assess any missed or new polyps. Subsequent endoscopic surveillance is based on the assessment of gastric cancer risk using a risk assessment tool (eg, OLGA) since virtually all of these patients have chronic gastritis.

Adenomatous gastric polyps (*gastric adenomas*) are usually solitary and most often occur in a background of chronic gastritis. Like colon adenomas, gastric adenomatous polyps have malignant potential and should be completely resected. The stomach should be diligently assessed endoscopically for metaplasia and dysplasia. Synchronous gastric cancer is not unusual with gastric adenomas, particularly if the adenoma contains a focus of adenocarcinoma. *Helicobacter* should be eradicated if present. Sessile and larger lesions are more likely to harbor dysplasia or cancer. Repeat endoscopy should be performed to ensure that other synchronous lesions were not missed and to assess adequacy of polypectomy. Subsequent endoscopic surveillance should be considered with frequency based on assessed gastric cancer risk.

Hamartomas can occur in the stomach in patients with Peutz–Jeghers (PJ) syndrome and PTEN hamartoma tumor syndrome (includes Cowden syndrome). If amenable to endoscopic removal this is not unreasonable, since carcinoma arising from hamartoma has clearly been described. Patients with PJ syndrome are at increased risk for gastric cancer (about 30% lifetime risk) but there is no evidence that removal of hamartomas decreases this risk, and the lifetime risk for colon cancer or pancreas cancer is even higher.
GASTRIC SUBEPITHELIAL TUMORS

Subepithelial gastric tumors include GIST (see Chapter 33), leiomyoma, lipoma, cyst, schwannoma, ectopic pancreas, and carcinoid (see below). They are identified on EGD or barium upper GI, and can best be evaluated by EUS and endoscopic needle biopsy with specimen evaluation by specialized immunohistochemical techniques. Symptomatic lesions should be removed. Incidentally discovered lipoma and cyst have characteristic EUS findings and do not require removal or close follow-up. GIST and leiomyoma have similar echo characteristics and both are spindle cell tumors on standard H&E stain, as is the less common schwannoma. These lesions are differentiated by immunohistochemistry: GIST is positive for c-kit; leiomyoma for desmin; and schwannoma for S100 protein. Regardless of symptoms, GIST is removed whenever possible either by endoscopic submucosal resection for small lesions, or laparoscopic or open gastric wedge resection. In the absence of worrisome EUS features such as irregular borders and internal heterogeneity, small leiomyomas (<2 cm) may be observed, but large leiomyomas (>5 cm) should be removed because of the risk of current or future malignancy. Intermediate lesions (2-5 cm) should be removed unless inconveniently located for wedge resection (eg, gastric cardia or prepyloric antrum), in which case diligent follow-up may be recommended on a case-by-case basis. Any change in the tumor is an indication for resection.

GASTRIC NEUROENDOCRINE TUMORS (CARCINOIDs)

The majority of gastric carcinoids (70%) are type 1 carcinoids and are enterochromaffin-like (ECL) neuroendocrine tumors that occur in the presence of hypergastrinemia due to atrophic gastritis, usually autoimmune (Table 29-11). They tend to be small and multiple with a low risk of malignancy. Endoscopic removal with biopsy of background gastric mucosa to confirm atrophic gastritis, and surveillance, is recommended. Antrectomy to remove the source of tumor-stimulating gastrin may be considered when there are multiple type 1 carcinoids larger than 1 cm or when recurrence is problematic. Type 2 carcinoids occur in the setting of gastrinoma and MEN-1. These lesions also tend to be multiple with a slightly higher risk of
malignancy, and the oxyntic mucosa is hyperplastic, not atrophic. Treatment is removal of the gastrinoma. If EUS and biopsy of type 1 or type 2 carcinoid show high-risk features (invasion of muscularis propria, angioinvasion, high mitotic count), gastrectomy is indicated. Type 3 carcinoid tumors are sporadic solitary tumors that occur in the setting of normogastrinemia. Malignant potential is high, and treatment is surgical resection with lymphadenectomy after clinical staging. Interestingly, there have been a few case reports of solitary and sizable gastric carcinoid tumors occurring in patients with hypergastrinemia without atrophic gastritis, associated with long-term PPI use.

**TABLE 29-11: MANAGEMENT OF GASTRIC NEUROENDOCRINE TUMORS (CARCINOIDS)**
Gastroparesis is a chronic gastric motility disorder defined by delayed gastric emptying of solids without evidence of mechanical obstruction. Diabetes is a recognized cause of gastroparesis. Primary idiopathic gastroparesis affects mostly young and middle-aged women who present with nausea, abdominal pain, early satiety, vomiting, fullness, bloating, anorexia, and weight loss, with nausea and vomiting being the most disquieting of all the symptoms.

Gastric neuroendocrine tumors (NETs)
Derived from ECL cells
Type 1 (70%-80% of gastric carcinoids)
  Occur in setting of hypergastrinemia from chronic atrophic gastritis usually autoimmune
  Typically multiple and small (<1 cm), commonly w background ECL hyperplasia
  Low malignant potential (5-year survival 95%)
  Consider EUS and endoscopic resection*
  Antrectomy to remove gastrin source in some patients
Type 2 (5%)
  Occur in the setting of hypergastrinemia associated w gastrinoma and MEN I
  Oxyntic mucosa is hyperplastic, not atrophic.
  Moderate malignant potential (5-year survival 70%)
  Consider EUS and endoscopic resection*
  Remove gastrinoma
Type 3 (20%)
  Usually solitary and large, often symptomatic, gastrin normal
  High malignant potential (5-year survival <50%)
  Poorly differentiated NET = “type 4” (1-year survival 50%)
  Perform EUS* and metastatic workup
  Consider gastrectomy with lymphadenectomy

*Gastrectomy and lymphadenectomy should be considered for lesions with high-risk features (vascular invasion, invasion of muscularis propria, high mitotic count, nodal involvement) which rarely may be present with type 1 carcinoid, and may be present in up to 30% of type 2 carcinoids.
Gastroparesis is diagnosed by symptom assessment and delayed gastric emptying of a solid meal. Gastric retention of more than 10% of the standard solid test meal at 4 hours is abnormal, with retention of more than 30% at 4 hours indicating severe gastroparesis.

Severe gastroparesis may result in recurrent hospitalizations, malnutrition, and significant mortality. Patients failing medical therapy (special diet and trial of promotility agents such as metoclopramide, erythromycin, and domperidone) are often considered for a variety of endoscopic and/or surgical interventions. In general, the therapeutic progression should start with the least aggressive interventions. Recent emphasis has been on reducing pyloric resistance with Botox, laparoscopic pyloromyotomy, or per oral endoscopic pyloromyotomy. Implantable gastric stimulators have helped some patients. Other options include gastrostomy, jejunostomy, gastrojejunostomy, and sleeve gastrectomy. Completion gastrectomy seems to provide symptom relief in post-surgical gastroparesis but this is generally considered a last resort.

**BEZOARS AND FOREIGN BODIES**

Bezoars are collections of undigestible matter that accumulate in the stomach and small bowel. They are the most common foreign body found in the stomach and may be seen in patients who have undergone prior gastric surgery, including after bariatric surgery. The most common bezoar is composed of hair (trichobezoars). It occurs most commonly in young women. Phytobezoars are composed of vegetable matter and are usually seen in association with gastroparesis or gastric outlet obstruction. Other types of bezoars include lactobezoars (concentrated milk formula), mixed medication bezoars (pharmacobezoars), and food bolus bezoars. Bezoars may present with obstruction, ulceration, or bleeding, and rarely as intussusception. Diagnosis is suggested by upper GI series and confirmed by endoscopy. Enzyme therapy with papain, cellulase, or acetylcysteine may be used, but most patients will need endoscopic or surgical disruption and extraction.

Foreign body ingestion in adults is usually associated with psychiatric or developmental disorder, intoxication, or incarceration. Repeated episodes of foreign body ingestion are common in some patients. Ingested foreign bodies are usually asymptomatic, but removal of sharp or large objects in the
stomach should be considered to avoid bleeding, perforation, or obstruction. Endoscopic removal of ingested foreign bodies is usually possible and is thought to be necessary in about 70% of intentional ingestions, while it is less frequently performed for accidental ingestion. Operation, open or laparoscopic, is performed in about 15% of adult patients with ingested foreign bodies, which most often are retrieved from the stomach. AP and lateral radiographs, and CT scan are helpful localizing studies. Contrast studies are avoided until the need for urgent endoscopy or operation is determined. For gastric foreign bodies, urgent removal is typically recommended for sharp pointed objects, objects longer than 6 cm, and magnets. Prompt but nonurgent removal is recommended for batteries and objects >2.5 cm. Airway protection is key, since aspiration of the foreign body during removal may occur. Retrieval of drug packets from the stomach of drug smugglers (“body packers”) is usually done surgically rather than endoscopically because the risk of rupture and dangerous overdose is thought to be lower with operation.

MISCELLANEOUS GASTRIC CONDITIONS

Dieulafoy Lesion

Dieulafoy lesion is a congenital arteriovenous malformation of the proximal stomach, typically on the lesser curve where it derives its supply from branches of either the left or right gastric artery. It is seen in middle-aged or elderly men and characterized by an unusually large, tortuous submucosal artery. Prior to widespread endoscopy, Dieulafoy lesions were diagnosed postoperatively but are now becoming diagnosed and treated routinely via endoscopy. It clinically presents as an upper GI bleed if eroded, and on endoscopy appears as a stream of arterial blood emanating from what appears grossly to be a normal gastric mucosa. Patients may also present with intermittent episodes of mild upper GI bleeding, and endoscopy can miss the lesion if it is not actively bleeding. Most lesions are now treated via endoscopic therapy (injection of epinephrine or other sclerosants, electrocoagulation, hemoclipping, rubber band ligation, and photocoagulation) or via angiographic embolization. Surgery is sometimes necessary, at which time the lesion may be oversewn or resected. Endoscopic
submucosal resection has also been reported. Dieulafoy lesions may occasionally be seen in the duodenum and jejunum as well as in the colon. These lesions have also been successfully managed via endoscopy or surgery.

**Gastric Diverticula**

Gastric diverticula are typically solitary and may either be congenital or acquired. Congenital diverticula are rare, true diverticula that typically occur near the gastroesophageal junction and are found on the lesser curve or in the posterior area. They will demonstrate all three layers of the gastric wall on endoscopic ultrasound. Acquired or pseudodiverticula usually have a negligible outer muscle layer and are due to either pulsion or traction, and most are found in the antrum. Symptoms are due to inflammation and may produce pain or bleeding, but perforation is rare. Symptomatic lesions should be removed, and this can be done laparoscopically.

**Mallory–Weiss Syndrome**

The Mallory–Weiss lesion is a longitudinal tear in the mucosa of the gastroesophageal junction, usually due to forceful vomiting and/or retching, and is commonly seen in alcoholics. It has also been reported after instrumentation of the esophagus and stomach. It typically presents with impressive upper GI bleeding. Endoscopy confirms the diagnosis and may be useful in controlling the bleeding, but 90% of patients stop bleeding spontaneously. In patients who continue to bleed, balloon tamponade, angiographic embolization, or selective infusion of vasopressin, systemic vasopressin, and surgery are other treatment options. At surgery, the bleeding lesion is oversewn via a long gastrotomy.

**Gastric Volvulus**

Gastric volvulus occurs when the stomach twists around one of its axes, usually seen with a large hiatal hernia. It can also occur in the unusually mobile stomach without a hiatal hernia. Typically, the stomach twists along its long axis (organoaxial volvulus), and the greater curvature flips up. Less frequently, it occurs around the transverse axis, called mesoaxial volvulus. It
is usually a chronic condition that can be surprisingly asymptomatic, and expectant nonoperative management is usually advised, especially in the elderly. The risk of strangulation and infarction has been overestimated in asymptomatic patients.

Surgery is recommended for symptomatic patients, especially if symptoms are severe and/or progressive. These patients complain of pain and pressure related to the intermittently distending and poorly emptying twisted stomach. Dyspnea, palpitations, and dysphagia may be seen due to compressive effects of the distended stomach on the surrounding organs. Symptoms are often relieved with vomiting or, if possible, passage of a nasogastric tube. The patient who presents moribund most likely has an infarcted stomach requiring urgent operation and resection, but this is quite unusual. Elective operation may often be done laparoscopically and usually involves reduction of the stomach, repair of hiatal hernia, and gastropexy. Gastropexy alone may be considered for high-risk patients or patients with short esophagus.

MINIMALLY INVASIVE GASTRIC OPERATIONS

The use of minimally invasive surgery in benign gastric diseases has seen a significant increase over the past decade. Minimally invasive techniques combined with either intraoperative endoscopic or radiologic localization are now routinely used for most localized, benign lesions such as leiomyomas, gastrointestinal stromal tumors (GISTs), and gastric diverticula. Combined endoscopic and laparoscopic techniques have also been described. The number and location of ports are determined by triangulating around the target organ, and most procedures can be performed using four to five ports. The benefits of laparoscopic surgery (less postop pain, quicker recovery, and decreased hospital stay) are all realized without compromising surgical principles of adequate resection and tension-free suture lines for many benign gastric disorders. Vagotomy (any type), patch closure of perforation, gastrojejunostomy, pyloroplasty, pyloromyotomy, and gastric wedge resection are all procedures that can and should be considered by the surgeon with advanced laparoscopic skills for the appropriate indication. Also, laparoscopic intragastric resection of large polyps or subepithelial tumors is a good option for lesions that are close to the pylorus or GE junction. An
anterior gastrotomy is made, the lesion identified and elevated, a GIA stapler placed across the base with apparent grossly negative margin, and then a 50-Fr bougie is passed per os through the GE junction to confirm patency. The stapler is fired, the lesion removed, and the anterior gastrotomy closed.

With the introduction followed by rapid improvements of the da Vinci robotic platform, the use of robotic technology, first in urology and gynecology, has now found increasing use in general surgical procedures. Despite its size, cost, and the lack of tactile feedback, the reported advantages over conventional laparoscopic surgery of improved ergonomics, tremor filtering, motion scaling, stable visual platform, and (wrist-like) instrument articulation, especially with the latest generation models (Xi system) have led to widespread adaptation in practice. Decreased conversions rates to open surgery (compared to laparoscopy) as well as expanding indications for a minimally invasive approach in more complex procedures (intracorporeal suturing, mediastinal/pelvis procedures) may be additional reasons for using the robot in gastric resection and reconstruction procedures, particularly those close to the pylorus or GE junction.

FURTHER READING

*Helicobacter Pylori Infection; Functional Dyspepsia*


Atrophic Gastritis


Peptic Ulcer Disease


Wilhelmsen M, Moller MH, Rosenstock S. Surgical complications after open and laparoscopic surgery...
Postgastrectomy Syndromes


Stress Ulcer Disease

Alshamsi F, Belley-Cote E, Cook D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer...


### Gastric Epithelial Polyps


### Gastric Subepithelial Tumors


### Gastric Neuroendocrine Tumors (Carcinoids)


Gastroparesis


Bezoars and Foreign Bodies


Miscellaneous Gastric Conditions


**Minimally Invasive Gastric Operations**


INTRODUCTION

In addition to being essential for adequate nutrient absorption, normal gastrointestinal motility is crucial for maintaining an appropriate balance of microorganisms and proper function within the gut. It also serves as a major defense mechanism against infection of the gut, and limits the propagation of bacteria to pathologic levels. Gastric atony, also referred to as gastroparesis, can be defined as the inability of the stomach to contract normally, causing a delay in the movement of food out of the stomach. Causal factors for gastric atony can be classified as either medical or idiopathic. The most common medical cause is diabetes mellitus, whereas less common medical conditions include neurologic disorders, connective tissue disorders, critical illness, and surgery.

In the nonsurgical patient with medical comorbidities, disruption of the normal motility can lead to atony, resulting in often devastating symptoms that severely impact nutrition and quality of life. Diabetic gastroparesis is thought to be the result of the dysregulation of the autonomic nervous system, a system that is intimately related to the neural functioning of the stomach. Similarly, the impact of neurologic disorders on gastric motility is often a...
consequence of the parallel functioning of neurotransmitters within the central nervous system and those found in enteric neurons. Disturbance of the former can lead to disruption of the latter and gastric atony. With connective tissue disorders, gastric atony is of critical importance, given the tendency of these patients to develop severe and complicated reflux resulting from lower esophageal sphincter hypotension and significantly impaired esophageal peristaltic amplitude. Critical illness greatly impairs the use of enteral nutrition and results in a sustained catabolic state that depletes the patient’s caloric reserves, leading to decreased immune function, impaired wound healing, and ultimately increased morbidity and mortality. This disruption can further result in bacterial overgrowth, translocation, pneumonia, and sepsis. While multiple therapeutic options exist for medical gastric atony, patients may often spend a majority of their life with discomfort and in search of the appropriate management.

In the postoperative setting, gastric atony, or failure of the stomach to empty, must, by definition, not be related to any other common postsurgical complication such as wound infection, intraperitoneal abscess, electrolyte disturbances, pancreatitis, thromboembolic disorders, pneumonitis, or cardiovascular complications. While a variety of factors may cause postoperative ileus, the specific categorization of atony must include “dysfunction causing a prolonged postoperative course defined as more than 14 days elapsing between the primary surgical intervention and planned discharge of the patient from the hospital.”

In general, there are a variety of techniques employed to treat gastric atony including medical management, endoscopic techniques, and surgical intervention. Future directions will focus on greater development of these treatment strategies either alone or in combination to improve the daily functioning of these patients. The purpose of this chapter is to review the biology, physiology, diagnosis, treatment options, and persistent clinical challenges that describe this often complex and debilitating disorder.

NORMAL GASTRIC MOTILITY

Research investigating the specific mechanisms through which the intestinal tract functions has revealed a well-designed balance between management of the intestinal microbiome and intestinal motility.
Historical Perspective

The role of the stomach in nutrient digestion and health maintenance has interested man since early times. The ancient Greeks often detailed the “bitter-sour” nature of gastric contents, and in the 16th century, both Paracelsus and van Helmont believed acid to be present in the stomach and a necessity for digestion. Subsequent observations by Reaumur and Spallanzani further described the “solvent” effects of gastric juices. However, the role of gastric acid was not well understood until 1823 when William Prout published his work on the effects of gastric acid secretion. Three years later, observations made by William Beaumont of his patient afflicted with a gastrocutaneous fistula, Alexis St Martin, were published in 1826. His detailed observations over almost a decade of the gastrocutaneous fistula described gastric digestion in a human during normal life experiences including the effects of stress.

In the early 20th century, the multifaceted nature of the control of gastric acid secretion was explored by experiments using ablation of the celiac axis and vagotomy as therapeutic intervention for peptic ulcer disease. This led to a rapid increased interest in gastric acid secretion and spurred the work of Dale and Laidlaw on histamine. This seminal research led to the critical discovery by Popielski of histamine’s effect on gastric secretion, Bayliss and Starling’s discovery of secretin, and Edkins’ discourse on gastrin. These discoveries ushered in a new era in our understanding of gastric disease and specifically led to remarkable advances in the pharmacologic management of peptic ulcer disease starting with the discovery of the H2-receptor antagonists by Sir James Black in 1972.

The emphasis on acid-related disease preoccupied research in the middle and latter half of the 20th century until the groundbreaking discovery of Helicobacter pylori in 1983 by Marshall and Warren. This was counterintuitive to the then current thinking that the stomach was microbiologically sterile, despite the many observations of numerous bacterial populations in gastric secretions described by Jaworski and the Nobel Prize–winning contribution of Metchnikoff in 1908 for his work describing Lactobacillus and gut immunity. As a consequence, the importance of the gastric microbiome and its relationship to H pylori revolutionized our understanding of gastric diseases, specifically cancer,
especially in terms of prevention. Current neurohormonal research has led to a better understanding of the control of appetite, food absorption, metabolism and obesity. Furthermore, increasing evidence supports a vital role for gastric motility in the maintenance of the several processes mentioned earlier in completing digestion and ultimately absorbing nutrients.

Current Understanding and the Migrating Motor Complex

Despite these many advances demonstrating the complexity of the stomach, it is still often viewed as “just” the hollow muscular organ that initiates the second phase of digestion (the first being mastication and transport of the food bolus through the esophagus). However, all ingested materials, specifically nutrients and orally dosed medications, have to negotiate the stomach, and as such, the stomach is now recognized to be one of the most important components within the gastrointestinal (GI) tract. Furthermore, the stomach facilitates many unique functions that are crucial to the continued transport of ingested materials, digestion, and the uptake of nutrition, roles that may also have a secondary purpose of maintaining homeostasis.\(^1,19,20\)

It is now confirmed that gastric motility is one of the most important factors necessary for normal digestion. In the interdigestive state, upper GI motility can be described by the recurrent contractility pattern of the migrating motor complex (MMC) (Fig. 30-1).\(^21\) The MMC is thought to serve a “housekeeping” role by sweeping residual undigested material through the digestive tract, out of the stomach, and into the small intestine. The MMC is a distinct 4-stage pattern of electromechanical activity that takes place in GI smooth muscle between meals. Although well preserved across mammalian species, the specific role of the MMC in humans has remained unclear. However, using manometry, Björnsson and Abrahamsson\(^22,23\) demonstrated that apart from the intestinal contractions migrating in the distal direction observed in phase II, phase III of the MMC also behaves as a retroperistaltic pump in the duodenum, creating intermittent alkalinization of the stomach. While acidity of the stomach has always been a key component of homeostasis, recent observations have also identified a role for this alkalinization in maintaining normal physiologic balance and signaling the return of hunger after meals.\(^24,25\) Conversely, impaired GI motility impedes
the absorption of drugs and nutrients introduced into the stomach, decreases the hunger stimulus, and can also be the nidus from which the symptoms of poor digestion, including nausea, vomiting, distention, and early satiety, begin.
GI motility serves as a major means to prevent infection of the intestinal tract. Normally, microorganisms are rarely encountered in the esophagus, stomach, and duodenum because of peristaltic contractions that continually move their contents toward the colon. While fairly low in the esophagus and stomach, the quantity of bacteria increases significantly as the GI contents reach the terminal ileum and eventually the bacterial-laden colon. Multiple “normal” physiologic processes within the gut limit the proliferation of these microorganisms to pathologic levels. While gastric acid is directly toxic to bacteria, resulting in minimized overgrowth, inhibiting gastric acid secretion in the face of normal motility does not seem to affect bacterial counts. Conversely, when motility is disrupted, with or without normal acid secretion, small intestinal bacterial overgrowth occurs. Hence, it is now recognized that patients with impaired GI motility are also at risk of bacterial overgrowth in the proximal gut with pathogenic organisms and subsequent translocation of these organisms or their toxins into the bloodstream.

We can conclude that normal GI motility is vital to the initial desire to eat, natural and timely digestion, the specific uptake of nutrients to maintain
health and well-being, and the regulation of bacterial flora whose structured concentration is also necessary for digestive stability. Disruption in motility at any step can have major consequences impacting overall health and nutrition in multiple ways.

CLASSIFICATION, PATHOPHYSIOLOGY, AND EPIDEMIOLOGY OF GASTRIC ATONY

Gastric atony can arise in multiple situations, including medical, postsurgical, and idiopathic settings, each related to specific derangements in normal motility (Table 30-1). The management of these patients presents several challenges and is best conducted in the context of a dedicated and skilled multidisciplinary team.

| TABLE 30-1: DIFFERENTIAL DIAGNOSES OF GASTRIC ATONY |
Medically Related Atony

DIABETES MELLITUS

Even though the relationship between diabetic gastroparesis and other complications of longstanding diabetes mellitus (DM) is incompletely understood, it has been established that there is an association with autonomic neuropathy. Additionally, although acute hyperglycemia delays gastric emptying, the relationship between long-term control of glycemia
and gastric emptying is unclear, and results from investigation have been conflicting at best. For example, although increased glycosylated hemoglobin (HbA1c) levels have been associated with GI symptoms in people with type 2 DM (T2DM), HbA1c levels were not found to be significantly different among patients with T2DM with GI symptoms and delayed gastric emptying, patients with T2DM with GI symptoms and normal gastric emptying, and patients with T2DM without GI symptoms. In addition, improved glycemic control did not improve gastric emptying in subjects with delayed gastric emptying and type 1 DM or patients with T2DM and delayed gastric emptying. These findings are in contrast to those of the Diabetes Control and Complications Trial (DCCT), in which 6.5 years of intensive insulin therapy reduced the risk of other complications such as diabetic retinopathy, nephropathy, and peripheral and cardiac autonomic neuropathy by 40% to 60% when compared with conventional insulin therapy. Furthermore, the differences between the former intensive and conventional treatment groups persisted for as long as 14 years despite the loss of glycemic separation. In the only community-based study, symptoms of peripheral or autonomic neuropathy were not associated with diabetic gastroparesis. Nevertheless, despite uncertainty in the causal factors for gastric atony, diabetic patients are still the cohort most commonly afflicted with medically related gastric atony, and are often most afflicted with gastric atony–related symptoms second only to patients with postsurgical gastric atony.

**NEUROLOGIC DISORDERS**

As populations age, the prevalence of neurologic disease continues to increase and consultations involving GI motility problems in the patient diagnosed with a neurologic disorder become ever more common. The high prevalence of gastric atony and other disturbances of gut motor function in neurologic diseases is based on similarities in morphology and function of the neuromuscular apparatus of the gut and that of the somatic nervous system. Furthermore, the basic organization of the enteric nervous system (ENS) (neurons, ganglia, glia, and ENS-blood barrier) and the ultrastructure of its components are similar to those of the central nervous system (CNS). Almost all neurotransmitters identified within the CNS are also found in enteric neurons. Thus, the concept of ENS involvement in neurologic disease should not come as a great surprise.
Dysfunction of the autonomic nervous system (an important modulator of enteric neuromuscular function) can be commonly seen in several neurologic syndromes. In addition to the presence of several primary and secondary disorders of autonomic function, disturbed autonomic modulation of gut motor function, in some cases, may be an important factor that contributes to symptom development. It is also evident that the gut has important sensory functions. Sensory input is fundamental to several reflex events in the gut, such as the viscerovisceral reflexes that coordinate function along the gut. Even though these functions are usually subconscious, gut sensation may be relayed to and perceived within the CNS. Because the role of sensory dysfunction in the mediation of common symptoms such as abdominal pain and nausea in the patient with CNS disease with GI manifestations has not been extensively investigated, this does offer a future area of study.

The two predominant neurologic disorders often encountered in GI practice are cerebrovascular disease and parkinsonism. In addition, patients with multiple sclerosis, autonomic and peripheral neuropathies including that associated with diabetic autonomic neuropathy, Guillain-Barré syndrome, myotonic dystrophy, and Duchenne muscular dystrophy have all been shown to demonstrate signs and symptoms suggestive of gastric atony. Regardless of the specific neurologic diagnosis, the use of a multidisciplinary team that is aware of the wishes and needs of the family and mindful of the nature and the natural history of the underlying disease process is best practice. Together, the team, including a neurologist and/or neurosurgeon, nutritionist, gastroenterologist, and specialty nurse, can assess and manage gastric atony and other GI problems in the patient with neurologic disease.

CONNECTIVE TISSUE DISORDERS

Gastric atony is also seen with scleroderma, one of the most common causes of pseudo-obstruction. Gastric involvement in scleroderma tends to parallel the same clinical course as the esophagus. In the Olmstead County study, 10.8% of all cases of definite gastric atony were associated with the presence of a connective tissue disorder. In scleroderma, gastric involvement has been documented in anywhere from 10% to 75% of all patients, and delayed gastric emptying has been seen in 50% to 75% of those patients with scleroderma who demonstrated GI symptoms. Gastric atony in itself has important clinical consequences in scleroderma, including
exacerbation of gastroesophageal reflux and malnutrition. The former is of critical importance, given the tendency of these patients to develop severe and complicated reflux resulting from significantly impaired esophageal peristaltic amplitude and lower esophageal sphincter hypotension. Using the relatively noninvasive $^{13}$C-octanoic acid breath test, Marie et al$^{40}$ documented delayed gastric emptying in 47% of 57 consecutive patients with scleroderma. Furthermore, they described a close correlation between GI symptoms and a delay in gastric emptying.$^{40}$

Using the same approach, Hammar et al$^{41}$ discovered atony in 29% of their 28 patients with primary Sjögren syndrome. Most recently, a reported association between Ehlers-Danlos syndrome type III (the joint hypermobility syndrome) and a variety of functional GI symptoms, including those that may be based on gastric emptying delay, have begun to emerge,$^{42-44}$ with the frank documentation of gastric atony in some of the studies.$^{42}$

**CRITICAL ILLNESS**

The prevalence of delayed gastric emptying in the intensive care unit (ICU) setting has been estimated to range from 38% to 57%, depending on the method used to define it.$^{45,46}$ Using the $^{13}$C-octanoate acid breath test and measuring $^{13}$CO$_2$ in end-expiratory breath samples, Ritz et al$^{47}$ found that 40% to 45% of the patients in an intensive care setting had delayed gastric emptying. Factors that can contribute to delayed gastric emptying in critical care patients include the supine position, coughing, suctioning, obesity, and advanced age, and the extent of the delay is directly related to the severity of critical illness. Nguyen et al$^{48}$ found that, after controlling for other factors, admission diagnoses had only a modest impact on the risk for gastric atony in the ICU, with those at the highest risk being patients with head injuries, multisystem trauma, sepsis, and burns. That being said, a number of comorbid conditions may increase gastric emptying time, including raised intracranial pressure, hiatal hernia, gastric cancer, gastric resection, liver cirrhosis, and chronic pancreatitis. Interestingly, Lam et al$^{49}$ observed in a retrospective study that a history of diabetes was not an independent risk factor for gastric emptying delay in critically ill patients despite its high prevalence in modern hospital populations. Additionally, proximal gastric motor responses to feeding were similar in diabetic patients to those of
healthy individuals. Nevertheless, hyperglycemia does impair gastric contractility and, along with electrolyte disturbances, may lead to gastric atony. Hence, in the critically ill setting, the continued need for optimization of both of these parameters is vital. Treatment has thus focused on the correction of electrolyte disturbances, withdrawal of medications that may impair gut motility, hypoglycemic monitoring, the addition of prokinetics, and the placement of feeding tubes (gastrostomy or jejunostomy) as needed.

**Postsurgical Atony**

Although many surgical procedures originally associated with gastroparesis or gastric atony are less commonly performed today, several more recently developed upper abdominal procedures may be complicated by the development of gastric atony (*Table 30-1*). Acute gastric atony may be the result of the “ileus syndrome,” which can complicate many surgical procedures. Most often, it is a transient event that usually resolves in a short period of time. Occasionally, this gastric dysmotility can become chronic and result in significant symptoms. In contrast to chronic medical gastric atony, whose pathophysiology is often poorly understood, in the acute form of postsurgical atony, inflammatory processes seem central to the inhibition of motility. The frequency of postsurgical gastric atony can vary widely depending on many factors including the site and nature of the surgical procedure. Again citing the prominent Olmstead County studies of the community prevalence of gastric atony, 7.2% of all cases were related to prior gastrectomy or fundoplication. More specifically, Dong and colleagues noted that the rates of atony ranged from 0.4% to 5% after gastrectomy, 20% to 50% after pylorus-preserving pancreaticoduodenectomy, and 50% to 70% after cryoablation therapy for pancreatic cancer.

**VAGOTOMY**

Although vagotomy is now infrequently performed for the management of peptic ulcer disease, the effect of inadvertent vagal injury underscores the continued relevance of a complete understanding of the complex effects of
vagotomy on gastric motor function. Loss of vagally mediated reflexes impairs receptive relaxation of the gastric fundus, leading to acceleration of the early phase of liquid emptying. This acceleration causes rapid emptying of hyperosmolar solutions into the proximal small intestine and may result in dumping syndrome. Conversely, and as a consequence of impaired antropyloric function, vagotomy prolongs the later phases of liquid and solid emptying. Other motility effects of vagotomy include impairment of the motor response to feeding, which contributes to the pathophysiologic mechanisms of postvagotomy diarrhea, and a suppression of the antral component of the MMC, which is particularly common among individuals with symptomatic postvagotomy gastroparesis.

Currently, standard practice includes the addition of a drainage procedure, such as a pyloroplasty or gastroenterostomy, which tends to only negate the effects of vagotomy and results in little alteration in the gastric emptying of liquids or solids. Interestingly, prolonged postoperative gastroparesis (ie, lasting longer than 3-4 weeks) is, in fact, rare (<2.5% of patients after either vagotomy and pyloroplasty or vagotomy and antrectomy). In contrast, significant postoperative gastric atony may occur in patients who have a prior history of prolonged gastric outlet obstruction. In these cases, normal gastric emptying may not return for several weeks. That being said, longitudinal studies suggest that vagotomy-related gastroparesis trends toward resolution over time. One study has suggested gastric emptying in those who had undergone either a truncal or a highly selective vagotomy (previously thought to have very different long-term results) being similar in clinical features by 12 months after the procedure.

When postsurgical gastric motor dysfunction persists, it can often present an arduous management challenge. Responses to medical therapies such as prokinetic agents have proved particularly disappointing in this group, and in these resistant cases, a completion gastrectomy may be the best alternative. It should be noted, however, that this intervention may still lead to frustration, as results in a large series deemed this approach successful in only 43% of patients.

ANTIREFLUX OPERATIONS

Multiple studies have documented that fundoplication affects sensorimotor function of the proximal stomach. Furthermore, most, but not all,
studies have demonstrated that following fundoplication, there is impaired relaxation of the proximal stomach in response to meal ingestion. Instances of gastric atony have been described following antireflux surgery and endoscopic antireflux procedures,\textsuperscript{61} even though the usual effect of fundoplication is to accelerate, rather than delay, gastric emptying.\textsuperscript{58} It should come as no surprise that Nissen fundoplication was the most common cause of postsurgical gastroparesis in the audit conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Consortium. Despite the high frequency with which this procedure is now performed,\textsuperscript{62} the pathophysiologic process leading to postfundoplication gastroparesis remains unclear. It has been proposed that some cases of postsurgical gastric atony have been secondary to an unrecognized preoperative disorder. In other cases, there is compelling evidence to implicate vagal nerve injury, which also has a higher occurrence in redo procedures and may contribute to persistent gas and bloating symptoms.\textsuperscript{63}

In rare instances, postfundoplication gastric atony may be severe and persistent. Although gastric resection does not seem to offer much help for these situations,\textsuperscript{64} some success has been reported with an approach that combines pyloroplasty with the conversion to a partial fundoplication.\textsuperscript{65} In an uncontrolled trial, endoscopic injection of the pylorus with botulinum toxin A produced symptomatic improvement in a small series of patients with postvagotomy gastroparesis, which in the vast majority was thought to result from fundoplication.\textsuperscript{66}

**ROUX-EN-Y SYNDROME, OR ROUX SYNDROME**

Patients undergoing creation of a Roux-en-Y gastroenterostomy can develop severe symptoms of postprandial abdominal pain, bloating, and nausea. This has often been associated with a specific clinical entity referred to as the Roux syndrome.\textsuperscript{67} Studies have inconsistently described impaired gastric motor function\textsuperscript{68} and a functional obstruction within the roux limb as a result of motor asynchrony,\textsuperscript{67,69} with the latter demonstrated by manometry. Regardless of these associations, for the most part, the overall impact of these motility patterns in the pathophysiologic processes of this syndrome still remains unclear.\textsuperscript{70}
BARIATRIC SURGERY

Ardila-Hani and Soffer\textsuperscript{71} comprehensively reviewed the impact of bariatric (or metabolic) surgical procedures on GI motor function and found that esophageal problems were by far, the most common. Gastric emptying did not appear to be affected by laparoscopic adjustable gastric banding, whereas Roux-en-Y gastric bypass and sleeve gastrectomy tended to accelerate gastric emptying. The few instances of gastric atony reported have often been described as severe and persistent and likely secondary to an anastomotic stricture, small bowel obstruction due to anastomotic edema of either the gastrojejunostomy (most common) or jejunojejunostomy, hernia, or behavioral problems such as disordered eating. Medical therapy appears to be the first-line approach; however, this too can result in lackluster alleviation of symptoms. Interestingly, Salameh et al\textsuperscript{72} described successful treatment using gastric electrical stimulation in 6 patients with intractable gastroparesis following Roux-en-Y gastric bypass for morbid obesity. More investigation will be needed before consistent solutions to this rare problem can be offered.

GASTRECTOMY

Symptomatic “dumping” may occur in up to 50% of patients after Billroth I or II gastrectomy. By removing the antral mill, antral resection often renders the stomach incontinent to solids, leading to accelerated emptying.\textsuperscript{73} Late dumping symptoms occur 90 to 120 minutes after a meal and are a consequence of reactive hypoglycemia. In addition, the accommodation reflex is impaired among symptomatic patients.\textsuperscript{74} Delayed gastric emptying sometimes occurs after a Billroth II gastrectomy as a result of a large atonic gastric remnant.\textsuperscript{73} Meng et al\textsuperscript{75} reported a 6.9% frequency of gastric atony among 563 patients who underwent radical gastrectomy for gastric cancer in their hospital in Shanghai, China. The principal risk factors for the occurrence of atony included preoperative gastric outlet obstruction and anastomotic function following reconstruction. While others have proposed laparoscopy-assisted, pylorus-preserving gastrectomy as a less radical operative approach to early gastric cancer, gastric atony was still the most common complication of this procedure, occurring in 6.2% of cases.\textsuperscript{76} Interestingly, Meng et al\textsuperscript{75} also observed a similar rate of gastric atony
(3.7%) among a smaller group of patients who underwent a laparoscopic gastrectomy. Reassuringly, in contrast to the previously mentioned experience with completion gastrectomy following vagotomy, completion gastrectomy has been shown to result in significant symptomatic improvement among subjects with postgastrectomy gastric atony.\textsuperscript{77}

**PANCREATECTOMY**

Pancreatectomy, pancreas transplantation,\textsuperscript{78} and pylorus-preserving pancreaticoduodenectomy, in particular, have been associated with a high incidence of postoperative gastric atony. Over time, it has been concluded, that while operative technique generally seems to be of less importance, the principal predictor of gastric emptying delay after these operations is the occurrence of other postoperative complications.\textsuperscript{79,80} Parmar et al,\textsuperscript{81} in what has been the largest series (N = 711) to date, documented an overall rate of delayed gastric emptying specifically following pancreaticoduodenectomy of 20%. Furthermore, they observed that the occurrence of gastric atony was associated with complications such as fistula formation, postoperative sepsis, and reoperation, and did not seem to be influenced by technical factors such as pylorus preservation or whether the gastrojejunostomy was antecolic or retrocolic. In contrast, results of a prior systematic review\textsuperscript{82} found that an antecolic reconstruction was in fact linked to lower rates of gastroparesis. Others have suggested that the use of a Billroth II rather than a Roux-en-y gastrojejunostomy for reconstruction following this procedure may reduce the risk of gastric emptying delay.\textsuperscript{83} Either way, decreasing the complication rate while paying attention to surgical technique may be helpful in decreasing postsurgical atony. Interestingly, the presence of preoperative diabetes has also been identified as an additional risk factor for this postsurgical cohort.\textsuperscript{84}

**OTHER PROCEDURES**

It has been demonstrated that virtually any procedure that can affect upper GI motor function or compromise the vagus nerve can result in gastric atony. Clinically significant atony or gastroparesis has been reported not only in association with a wide range of gastric procedures but also in relation to esophageal procedures including botulinum toxin injection for achalasia\textsuperscript{85} and esophageal resection,\textsuperscript{86} lung transplantation, and even hepatic surgery.
Sutcliffe et al\textsuperscript{86} noted a 12% rate of gastric conduit emptying delay in a series of patients following esophagectomy. In another report, gastric atony was more commonly seen after minimally invasive than open esophagectomy.\textsuperscript{87} Gastric atony in the setting of lung transplantation is especially worrisome, as its presence preoperatively has been associated with an increased risk for the development of bronchiolitis obliterans syndrome.\textsuperscript{88} Although common even before surgery,\textsuperscript{69} new-onset gastric atony has also been observed in up to 6% of subjects after transplantation\textsuperscript{88,89} and may trigger or exacerbate gastroesophageal reflux from which these patients have no protection. For this reason, there is a low threshold in this patient population to proceed with fundoplication in combination with gastric electrical stimulation to address concomitant gastric atony.\textsuperscript{90}

**Idiopathic Atony**

Among patients who do not have underlying disorders or have not undergone any of the surgical procedures described above, the pathogenesis of idiopathic gastric atony is poorly understood, but often still has some link to illness or remote surgery. In a tertiary referral series of patients with idiopathic gastric atony, it was observed that the onset of symptoms was consistent with a viral origin in 23% of participants.\textsuperscript{91} In the NIDDK Gastroparesis Clinical Research Consortium, approximately 19% of participants with idiopathic gastric atony and 14% with either type 1 DM or T2DM and gastric atony demonstrated symptoms of an infectious prodrome before diagnosis.\textsuperscript{92} Although cholecystectomy, per se, has not been incriminated as a cause of gastric atony,\textsuperscript{36} a prior cholecystectomy seems to negatively affect the natural history of both diabetic and idiopathic gastroparesis. The previously mentioned tertiary study found that gastroparesis symptoms began after a cholecystectomy in 8% of participants,\textsuperscript{93} and 36% of patients with idiopathic or diabetic gastric atony had undergone a cholecystectomy in the NIDDK study.\textsuperscript{92} Whether cholecystectomy is an independent risk for atony is unclear; however, patients with cholecystectomy had more comorbidities, particularly chronic fatigue syndrome, fibromyalgia, depression, and anxiety.
Hospitalization and Economic Burden

Hospitalizations with gastroparesis as the primary diagnosis increased from 3977 in 1995 to 10,252 in 2004 (+158%), whereas hospitalizations with gastroparesis as the secondary diagnosis increased from 56,726 to 134,146 (+136%). In contrast, smaller changes were seen in diabetes-related hospitalizations (+53%), all hospitalizations (+13%), and hospitalizations with gastroesophageal reflux disease (GERD), gastric ulcer, gastritis, or nonspecific nausea/vomiting as the primary diagnosis (~3% to +76%). Furthermore, comparing 4 of the most common GI conditions (GERD, gastric ulcers, gastritis, and nonspecific nausea/vomiting), when gastric atony or gastroparesis was listed as the primary diagnosis, the length of stay was longer (increase of 15.4%-66.2%; all conditions vs gastroparesis, *P* < .001) and had the highest or second highest total charges (~7.2% to +60.6%, all *P* < .01) in 2004, with similar results in 1995. Although more recent trends have yet to be published, similar trends for gastric atony versus other diagnoses have been previously observed.

Bielefeldt et al pointed at an indirect economic impact of the chronic illness with high rates of un- or underemployment and likely, as a result, a high number of patients with low household incomes. Parkman et al more recently published a study of nearly 400 patients demonstrating that while patients reported median household incomes close to the national average, less than half of the patients were employed at the time of enrollment and nearly one-third had high rates of work absenteeism due to their disease.

CLINICAL PRESENTATION

Signs and Symptoms

As previously mentioned, the symptoms of gastric atony can be frustrating and debilitating for the patient. While some are able to find intermittent relief, others may toil for years, resulting in a substantial decrease in quality of life.

NAUSEA AND VOMITING
Regardless of the etiology, nausea and vomiting are the most common symptoms in patients with gastric atony, with over 40% of patients reporting that these symptoms are among the most bothersome. Accordingly, the pathogenesis of these symptoms is heterogeneous and often multifactorial. It is known that the receptor site for vomiting is centrally located in the area postrema at the base of the fourth ventricle in the brain (chemoreceptor trigger zone). Peripheral receptor sites include the vagus nerve and vestibular apparatus. Stimulation of the vagal afferents from either gastric distention or deregulated gastric motility triggering emesis can lead to a repeated cycle of vomiting following the first episode.

**EARLY SATIETY AND FULLNESS**

Early satiety and fullness are common symptoms among patients with both idiopathic and diabetic gastric atony, especially in those with T2DM. Impaired gastric accommodation, known as the reduction in gastric tone and increase in compliance that follows ingestion, has been found in 43% of patients with idiopathic gastric atony, and it contributes to patients’ inability to completely tolerate a normal meal. Similarly, impaired gastric accommodation was found in 40% of patients with functional dyspepsia. A smaller study of 10 diabetic gastroparesis patients, who were refractory to prokinetic therapy, found that 90% of these patients had impaired gastric accommodation.

Several medications have been shown to increase gastric accommodation in healthy subjects as well as patients with functional dyspepsia. Notably, buspirone was shown to result in improvements in functional dyspepsia symptoms, particularly postprandial fullness, bloating, and early satiety.

**BLOATING**

Bloating is another common symptom seen in functional GI disorders such as irritable bowel syndrome (IBS) and functional dyspepsia along with gastroparesis. Although there has been no association found between the rate of gastric emptying and severity of bloating, the presence of bloating with gastroparesis has been associated with a poor response to medical therapy. A large multicenter study including 335 patients found that
bloating was present in 76% of patients with gastric atony, with 41% suffering severe symptoms. Interestingly, it was found that there was also an association between the use of norepinephrine reuptake inhibitors (predominantly tricyclic antidepressants) and symptoms of mild bloating.

ABDOMINAL PAIN

Although abdominal pain is a common feature of gastric atony, studies have consistently shown that the severity of pain also does not correlate with the severity of the delay in gastric emptying. Specifically in diabetic patients, pain predominance was found in approximately 20% of patients referred to the NIDDK Gastroparesis Clinical Research Consortium. Visceral hypersensitivity, defined as a lowered threshold for eliciting visceral pain, is common among functional GI disorders, including functional dyspepsia, IBS, and gastroparesis. The presence of visceral hypersensitivity was found in 29% of patients with idiopathic gastric atony and 55% of patients with diabetic gastric atony. The presence of hypersensitivity to intragastric balloon distention was associated with a higher prevalence of abdominal pain, early satiety, and weight loss. Similarly, among these gastroparesis patients, the presence of hypersensitivity was also associated with greater symptom severity.

DIAGNOSIS

Radiologic (Gastric Emptying and Scintigraphy)

The gold standard for quantifying gastric emptying is gastric emptying scintigraphy, and the consensus recommendations for the procedure involve technetium-99m sulfur-colloid labeled, low-fat, egg-white meal with imaging at 0, 1, 2, and 4 hours. The diagnosis of delayed gastric emptying is confirmed if there is >90% gastric retention at 1 hour, >60% at 2 hours, and >10% at 4 hours. This test is noninvasive, widely available, and easy to perform. Other routine tests include upper abdominal x-ray and esophagastroduodenoscopy (EGD) to rule out mechanical obstruction. Real-time magnetic resonance imaging (MRI) has also been shown to be a reliable tool for the assessment of gastric motion; however, the study itself is
expensive, time intensive, and not widely available.\textsuperscript{108,110,111}

**Manometry and Electrogastrography**

Gastric manometry is an invasive test that measures motility patterns of the gut. This test requires expertise to perform and evaluate the results. Gastric manometry can reveal characteristic patterns that suggest a neuropathy, myopathy, or intestinal mechanical obstruction.\textsuperscript{111} Electrogastrography, a noninvasive measurement of electrical activity of the gastric smooth muscle, is used predominantly in research to evaluate for gastric arrhythmias.\textsuperscript{109} Electrogastrography measures electrical rhythms, but because it requires expertise to evaluate results, it is not widely available.\textsuperscript{108,111}

**TREATMENT OPTIONS**

Optimal treatment can only be achieved once a careful investigation has taken place to properly diagnose gastric atony, exclude iatrogenic causes, correct electrolyte or metabolite imbalances, and modify eating habits and diet to achieve the peak level of noninvasive symptom relief possible. While medical management has been the gold standard initial treatment for most cases of gastric atony, the emergence of minimally invasive techniques has created attractive alternative options for patients who do not respond to medical management. When all else fails, conventional surgical remedies can be considered. **Figure 30-2** offers a treatment algorithm for patients with symptomatic gastroparesis.
FIGURE 30-2 Treatment algorithm for gastric atony. While medical management has been the gold standard regarding initial treatment for most
cases of gastric atony, the emergence of minimally invasive techniques has created attractive alternative options for patients who do not respond to medical management. Conventional surgical remedies can be considered if other options fail. GES, gastric electrical stimulation.

**Medical Therapy**

Although a multitude of pharmacologic therapies exist for the treatment of gastroparesis, prokinetic agents are by far the most recognized agents. It has been approximately 30 years since the first randomized controlled trials of the conventional prokinetic agents, metoclopramide, domperidone, and erythromycin, have been published. Despite this, they are still the first-line agents for the treatment of gastroparesis.\(^{112}\) Much like many other investigated areas of gastric atony, the majority of data regarding the efficacy of conventional prokinetic agents for the treatment of gastric atony are outdated.\(^{113-117}\) Metoclopramide has been the most extensively studied and has been associated with less improvement in gastric emptying when compared to the macrolide antibiotic erythromycin.\(^{117}\) A meta-analysis assessing the benefits of 4 different medications in 514 patients in 36 clinical trials reported erythromycin as the most potent stimulant of gastric emptying. Both erythromycin and the dopamine receptor antagonist domperidone (not available in the United States) are best at reducing the symptoms of gastric atony.\(^{118}\) Currently, several novel pharmacotherapies such as ghrelin receptor agonists (TZP-101, TZP-102, RM-131), mitemcinal, prucalopride, velusetrag, and levosulpiride are in development; however, their clinical efficacy and safety still need to be determined.\(^{112,119,120}\) While it is generally accepted that a significant percentage of patients require additional therapy beyond prokinetic agents, no clear data exist to determine the percentage of patients who fail medical management. Nevertheless, the use of promotility drugs in all patients is a relatively safe and effective means to circumvent the problem of gastric atony and improve patient recovery. Furthermore, understanding the drugs available and their interaction with the receptors involved in neuromuscular transmission within the GI tract can often aid the clinician in selecting the optimal therapy.

**Endoscopic Techniques**
Gastric atony has traditionally been a largely medically managed disease with refractory symptoms typically falling under the umbrella of the surgical domain. Advancements in the field have included the endoscopic management of gastroparesis, which most commonly involves intrapyloric botulinum toxin A injection and gastric electrical stimulation implantation. Furthermore, on the horizon are novel endoscopic approaches that have the potential to radically improve the standard of care. Endoscopic management of gastroparesis seeks to treat delayed gastric emptying with a less invasive approach compared to traditional surgical approaches.\textsuperscript{121} New endoscopic procedures offer a minimally invasive alternative to more radical options and should probably be more widely adopted. However, a progressive algorithm needs to be followed in challenging cases: starting with medical treatment and diet modification, then progressing through endoscopic treatments including new interventions such as per-oral pyloromyotomy, and finally using laparoscopic and/or open interventions including gastrectomy for truly refractory cases.\textsuperscript{122}

**BOTULINUM TOXIN A (BOTOX)**

Botulinum toxin A inhibits neuromuscular transmission. It has become a drug with many indications for several neurologic and nonneurologic conditions. One of the most recent achievements in the field is the observation that botulinum toxin A provides benefit in diseases of the GI tract. The toxin blocks cholinergic nerve endings in the autonomic nervous system but does not block nonadrenergic noncholinergic responses mediated by nitric oxide. This has promoted further interest in using botulinum toxin A as a treatment for overactive smooth muscles and sphincters. The introduction of this therapy has made the treatment of several clinical conditions, including gastroparesis, easier in the outpatient setting, at a lower cost and without permanent complications.\textsuperscript{123} However, the benefits of botulinum toxin injections in gastric atony have been unclear. Several retrospective and open-label studies have shown clinical advantages of intrapyloric botulinum toxin type A injections, whereas other smaller randomized trials did not show positive results. Overall, the available published studies have yielded conflicting results, leading to a fading out of Botox therapy for gastroparesis.\textsuperscript{124} Currently, the American Gastroenterological Association (AGA) does not recommend the use of endoscopic Botox for patients with
gastroparesis.\textsuperscript{125} However, given the small sample size of existing studies with conflicting data, there is a continued need for larger randomized trials in the future before a definitive decision or treatment guidelines can be established.

**ENDOSCOPIC GASTRIC STIMULATOR IMPLANTATION**

In 2000, gastric electrical stimulation (GES) was approved by the US Food and Drug Administration (FDA) as a humanitarian device exemption in patients with refractory symptoms of diabetic or idiopathic gastroparesis.\textsuperscript{126} Often referred to as a gastric pacer, GES uses an implantable device consisting of a pulse generator that allows for electrical stimulation at a variety of frequencies. Permanent GES for gastroparesis typically requires a surgical implantation under general anesthesia. Several case series and small randomized controlled trials, the most important being the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS), have shown clinical benefit from GES.\textsuperscript{127-133} A subsequent meta-analysis by Chu et al\textsuperscript{134} in 2012 confirmed significant improvement in symptom severity and gastric emptying times, although many of the analyzed studies were low-quality observational studies lacking control groups. A more recent study by McCallum et al\textsuperscript{130} also demonstrated improvement in weekly vomiting frequency among all patients with idiopathic gastric atony with a median reduction of 61.2%. The National Institute of Health and Care Excellence issued guidelines in 2014 that stated that the current evidence is adequate to support the use of GES.\textsuperscript{135}

Up until 2012, surgery was the only available means to implant the GES device. Endoscopic placement of temporary gastric stimulators has been proven as a concept and is often used to determine whether a patient will respond to GES before undergoing a permanent implant surgery. The lack of a permanent endoscopic solution and the reliance on surgical implantation for symptomatic improvement has at present limited further endoscopic utilization.\textsuperscript{136,137} However, Deb et al\textsuperscript{138} designed 5 innovative endoscopic gastric implantation techniques and developed a novel, wirelessly powered miniature gastrostimulator. Although this early model has only been evaluated in pig investigations, the studies provide a promising prototype for
other dysmotility treatment paradigms and exciting new options that may translate in the future to less invasive endoscopic placement in gastroparetic patients.\cite{139}

**SURGICAL IMPLANTATION OF GASTRIC ELECTRICAL STIMULATION**

The implantation procedure of the GES can be performed via laparotomy or a laparoscopic approach. Two intramuscular leads containing electrodes (Model 4351; Medtronic) are inserted into the muscularis propria of the stomach.\cite{140,141} The 2 electrodes are sutured 9 and 10 cm from the pylorus on the greater curvature of the stomach and connected by leads of 35 cm in length to the pulse generator, which is placed subcutaneously in the abdominal wall, usually in the right upper quadrant. The programming parameters are usually set as the default at surgery and are then reevaluated approximately 3 months after surgery. While some investigators have proposed specially designed algorithms,\cite{142,143} due to the lack of any controlled trials, these have only been used for clinical nonresponders. In a 10-year observation,\cite{144} it has been shown that the electrical current is increased approximately 20% to 30% during follow-up interrogations based on a clinician observation that symptoms are not optimally controlled and more voltage might help. However, this practice has not been based on any supportive evidence.

**ENDOSCOPIC PYLOROMYOTOMY**

Rao et al\cite{145} demonstrated that phasic motor activity in the antrum and duodenum can be stimulated by fundic balloon distention. While there are no such studies to determine the effect of pyloric channel distention on the interstitial cells of Cajal in the stomach or gastric emptying, endoscopic pyloromyotomy and manipulation of the pylorus may improve gastroparesis refractory to medical management. Khashab et al\cite{146} demonstrated the feasibility and efficacy of this approach with a case report of the first human gastric per-oral endoscopic myotomy in a patient with severe refractory gastroparesis. The procedure was well tolerated with vast improvement in gastroparetic symptoms noted at 12-week follow-up.

This technique is similar in principle to the submucosal dissection and
myotomy performed for the treatment of achalasia.\textsuperscript{147} With this technique, endoscopy is performed and myotomies of the inner circular and oblique muscle bundles 2 to 5 cm proximal to the pylorus on the anterior wall of the stomach are performed. The longitudinal muscle layers are preserved. Endoscopic pyloromyotomy is then performed by dissecting the pylorus until deeper layers become evident with full separation of the pyloric ring.\textsuperscript{146,148}

Complications of endoscopic pyloromyotomy include GI bleeding, leak, and pneumonia.\textsuperscript{148} Despite these complications, the endoluminal pyloromyotomy technique could provide an incision-less, less invasive alternative with similar functional outcome as compared to standard laparoscopic or open pyloroplasty.\textsuperscript{148} While the small number of cases certainly limits the ability to determine the true impact of this procedure in the management of gastroparesis, with more frequent use, increasing technical experience, and more data, endoscopic pyloromyotomy has exciting potential to be at the forefront in the endoscopic management of gastroparesis.

**ENDOSCOPIC DECOMPRESSION OR BYPASS: PERCUTANEOUS GASTROJEJUNOSTOMY AND JEJUNOSTOMY**

Enteral nutrition and feeding is sometimes required for more severe symptoms of gastric atony and can be seen in up to 30\% of patients with grade 3 gastric atony.\textsuperscript{149,150} Specifically, a feeding jejunostomy is a critical adjunct to the treatment of gastroparesis as a means to maintain hydration, nutrition, and glycemic control. While surgical gastrojejunostomy is a potential treatment option for patients with refractory gastric atony, the procedure is associated with substantial morbidity and mortality when patients are in a less than ideal clinical condition.\textsuperscript{151-154} Furthermore, although surgical gastrojejunostomy has been shown to improve gastroparetic symptoms, endoscopic ultrasound-guided gastrojejunostomy using a stent has been developed but warrants further investigation due to unknown long-term stent safety and patency issues.\textsuperscript{152} Ideally, the stent can be removed after an interval of time, leaving a permanent fistula tract. However, studies are needed to determine the necessary pressure gradient and initial gastrojejunostomy tract diameter in order to maintain long-term fistula
patency after stent removal. The minute amount of data available to date, while optimistic and potentially transformative, requires repeat analysis and trials with human study before implementation into the gastroenterologist’s everyday arsenal. However, given the technical success reported in the studies above, the future of endoscopic gastrojejunostomy using EUS-guided lumen-apposing metal stents is bright, with the potential to diminish the need for invasive surgeries and improve symptoms of gastroparesis refractory to medical management.

Percutaneous endoscopic gastrostomies with jejunal extensions (PEGJ) are technically less demanding to perform but plagued with the difficulties of tube migration back into the stomach. One of the major negatives of percutaneous endoscopic jejunostomies (PEJs) is that the tube is generally positioned in the distal duodenum or very proximal jejunum and the force of active vomiting often leads to displacement or coiling of the tubing back into the proximal duodenum or the stomach, resulting in the enteral fluid being vomited. It also partially compromises the lumen size of the pylorus. This specific aspect is relevant because, as oral intake is introduced and PEJ feedings are being tapered off, the usually 14- to 16-Fr tube is still located in the pylorus, interfering with the gastric emptying process and the mechanism of the pylorus. The skin site is often also more difficult to manage because of the larger tube diameter with seeping or discharge of very acidic fluids onto the skin. The tube is large and needs to be secured to the skin and is painful and very cosmetically obtrusive.155

Direct percutaneous endoscopic jejunostomy (DPEJ) is a push enteroscopy technique that was first described by Shike et al156 and offers another option of providing direct postpyloric enteral nutritional support. In the largest cohort study to date, Maple et al157 reported clinical outcomes with DPEJ and included 307 attempts at PEJ placement with a success rate of 68%. Although this study included multiple indications for DPEJ placement, gastric atony comprised 21% of the cases. A case series by Toussaint et al158 showed a PEJ technical success rate of 78.6% with no immediate complications reported. However, this was based on a small sample size of only 14 patients. Based on these data, PEJ should be considered in the algorithm of enteral access for nutritional support before considering surgical jejunostomy. The main limitation of DPEJ is the technical difficulty of the procedure as the jejunum is narrow, making it more difficult to advance a needle directly into the
This difficulty can be alleviated with balloon-assisted enteroscopy (BAE)\textsuperscript{160}.

PEJs are technically more difficult to place but provide a more direct route for enteral alimentation without the need for laparotomy. Fan et al\textsuperscript{161} reported the outcomes of PEGJ versus PEJ with findings for reintervention rates of 39.5\% versus 9.0\%, respectively. Toussaint et al\textsuperscript{162} reported on the use of PEJ for gastroparesis with a success rate of 78.6\% and a complication rate of 36.4\%, including jejunal volvulus and jejunoocolic fistula. In summary, jejunostomies are a critical adjunct to the management of gastroparesis but need knowledgeable medical support to minimize long-term complications.\textsuperscript{155}

**SURGICAL GASTROSTOMY AND JEJUNOSTOMY TUBE PLACEMENT**

The theory that gastric tube placement is needed to provide venting in patients with gastroparesis to alleviate symptoms has not been proven to be beneficial. The abdominal bloating that patients with gastric atony experience has now been determined to be secondary to small bowel bacterial overgrowth, rather than the accumulation of air. Tube venting may also cause electrolyte imbalance, particularly potassium, which can become a major health risk. More importantly, patients may claim they have the ability to eat a meal, but the process of draining their intestinal contents by suction or venting can be a misleading indication of the patients’ progress. Additionally, it can often become an addictive habit. Intestinal venting can compromise the patient’s nutritional status by draining out the consumed nutrients and may also inhibit the stomach itself by not allowing it to adequately reeducate itself and regain motor function.\textsuperscript{155}

Gastrostomy and jejunostomy tubes can also be placed surgically through a mini-laparotomy, laparoscopically or endoscopically as previously mentioned. The largest series of gastroparesis (26 patients) followed with jejunostomy was studied by Fontana and Barnett,\textsuperscript{163} who demonstrated subjective perception of improved health with improved nutrition in 57\% of patients and decreased hospitalizations in 52\%. However, this series notably had 23 major complications requiring hospitalization and surgery, including intestinal obstruction, tube dislodgement, wound abscesses, and cellulitis,
reiterating that morbid complications can still occur despite the ease with which these tubes are placed.\textsuperscript{164}

Surgical jejunostomy tube placement can be performed concomitant to gastric surgery for gastroparesis. The 3 most common techniques are a longitudinal Witzel tunnel, the Roux-en Y technique, and the needle catheter technique. The Witzel technique involves creating a longitudinal tunnel in the small bowel wall that covers a several-centimeter length of tube so that inadvertent tube dislodgement facilitates the collapse and sealing off of the enterostomy.\textsuperscript{165} Gerndt and Orringer\textsuperscript{166} demonstrated that the routine use of the Witzel tunnel resulted in complications in only 2.1% of 523 patients. These complications included intestinal obstruction, intraperitoneal leak, and local and intra-abdominal abscesses.\textsuperscript{166} The Roux-en-Y jejunostomy has few indications and is mostly used for pediatric patients with severe injury and neurologic malformations.\textsuperscript{167} However, a high rate of complications was described, with 15% stoma prolapse and 6% leakage rates.

The needle catheter technique involves the use of the Seldinger technique whereby a needle is tunneled through the intestinal serosa and submucosal space for a distance of 5 cm before entering the enteric lumen. A wire is then passed through the needle followed by a narrow lumen catheter. Needle catheter jejunostomies are often used for feeding after oncologic procedures but are also plagued by complications, including tube blockage, tube dislodgement, and pneumatosis. However, Meyers and colleagues\textsuperscript{168} reported on the findings of 2022 patients with needle catheter jejunostomies and noted complications in only 1.5% of patients. The laparoscopic approach can also use the needle catheter technique for jejunostomy placement, resulting in small incisions and early return of bowel function with similar complications.

**TRANS PYLORIC STENTING**

An innovative approach recently described by Clarke et al\textsuperscript{169} involves the use of through-the-scope transpyloric stent placement as a treatment for gastric atony. In this small case series (n = 3), double-layered, fully covered Niti-S self-expandable metallic stents (TaeWoong Medical, Seoul, South Korea) were used and shown to successfully improve symptoms of gastric atony. The procedure entails the placement of a self-expandable stent across the pyloric channel. The stent is placed using endoscopic guidance without fluoroscopy. The stent is then fully deployed in the transpyloric position with
its proximal end in the gastric antrum. In all 3 cases, patient symptoms markedly improved or became asymptomatic at 115, 122, and 174 days of follow-up, respectively. While this was a case series of only 3 patients, the stark improvement and lasting results at follow-up after the procedure suggest that transpyloric stent placement may improve symptoms associated with impaired gastric emptying.\textsuperscript{169}

A major concern with transpyloric stenting is stent migration leading to intestinal obstruction or the recurrence of symptoms. Several stent-securing methods such as endoscopic clips (through-the-scope clip and over-the-scope clip) and endoscopic suturing have been described to reduce stent migration. However, at present, the question still remains regarding which stent-securing method is superior.\textsuperscript{170} Future studies are required to truly ascertain the long-term durability, utility, and preferred method for transpyloric stenting and fixation. Until that time, transpyloric stenting will remain a limited option for endoscopists in the management of patients with refractory gastroparesis.

**SURGICAL TREATMENT**

Surgical therapies for patients with intractable gastric atony have traditionally been reserved for patients who have failed diet modification, medical therapy, and/or endoscopic therapy. However, depending on the precipitating factor, surgical treatment may at times be warranted. Surgical options including pyloroplasty and gastrectomy (subtotal or total), along with electrical stimulation, or placement of gastrojejunostomy or jejunostomy feeding tubes are viable solutions.\textsuperscript{171}

**Pyloroplasty**

Pyloroplasty is beginning to emerge as a successful drainage procedure for refractory gastric atony in the surgical management of diabetic and nondiabetic gastric atony. A retrospective study was performed of 46 patients undergoing pyloroplasty for refractory gastroparesis.\textsuperscript{172} Modifiers of improvement included pre- and postoperative assessment using gastric emptying scintigraphy and the Gastroparesis Cardinal Symptom Index. Laparoscopic pyloroplasty was performed in 42 patients, open pyloroplasty was performed in 3 patients, and 1 patient was converted from a laparoscopic
to open pyloroplasty. Studies were repeated during the 6- to 12-month postoperative intervals. The postoperative gastric emptying scintigraphy improved in 90% of patients and normalized in 60%. Postoperative half-emptying time was significantly reduced ($P = .001$), as was the 4-hour retention ($P < .001$). The Gastroparesis Cardinal Symptom Index showed statistically significant reduction in symptom severity for all 9 categories ($P < .0005$) as well as total symptom score ($P < .005$), and no patients developed dumping syndrome. This has led to the conclusion that pyloroplasty is a highly effective therapy for refractory gastroparesis, offering significant reduction in symptom severity, improvement in quality of life, and acceleration of gastric emptying.

**Surgical Implantation of Gastric Electrical Stimulation with Pyloroplasty**

The lack of acceleration of the delayed gastric emptying by GES begs the question as to how much better the outcome would be if gastric emptying could be accelerated. This is the rationale for the addition of a surgical pyloroplasty (PP) performed at the time when GES is implanted. This approach can be supported by the following data in the literature: first, the injection of Botox into the pylorus causes a transient but substantial decrease in symptoms and gastric retention rate, with this effect being the most pronounced in the postvagotomy subset$^{173}$; second, surgical investigation$^{174,175}$ has suggested that PP alone could have a role in patients with gastroparesis; and finally, pyloric spasm is hypothesized to be present in diabetes.$^{176}$ A subset of patients with idiopathic gastroparesis was suspected of having pyloric dysfunction based on pyloric motility findings.$^{177}$

Only 1 clinical investigation has tested whether PP combined with GES could enhance the outcomes of GES.$^{164}$ This study showed that gastric emptying improved in all subgroups, especially in postsurgical patients with gastroparesis. In fact, >50% of patients normalized their gastric emptying test. No adverse events related to the additional surgery were observed. In addition, oral intake and nutritional status were improved after PP with GES, along with a continued reduction in nausea and vomiting. A randomized, double-blind study would be beneficial to further confirm these excellent results. In general, it may be concluded that the addition of a Heineke-
Mikulicz PP to the standard GES procedure markedly improves and often normalizes delayed gastric emptying, especially in postvagotomy gastroparetic patients, thus enhancing long-term symptom control and augmenting the central mechanism of nausea and vomiting by GES. Furthermore, the data would support that PP should be recommended to be routinely added to the standard GES procedure.

**Total and Subtotal Gastrectomy**

Gastrectomy has traditionally been reserved for patients who have experienced severe refractory postsurgical gastric atony. Common operations resulting in postsurgical gastric atony include vagotomy for ulcer disease, Nissen fundoplication for severe GI reflux, the Billroth I and II gastric reconstructions for ulcer disease and gastric cancer, and the Whipple procedure, as previously discussed. Forstner-Barthell et al reported that extensive subtotal or completion gastrectomy provides symptomatic improvement in 67% of gastroparesis patients but has not always been shown to be beneficial in terms of weight gain. Nausea, the need for total parenteral nutrition, and retained food at endoscopy were negative prognostic factors for patient outcome following the procedure. Like other surgical adjuncts, complications were common (40%) and included narcotic withdrawal syndrome (18%), ileus (10%), wound infection (5%), intestinal obstruction (2%), and anastomotic leak (5%). Symptoms were relieved in 43% of participants (Visick grade I or II); however, 57% of candidates remained in Visick grade III or IV. Nausea, vomiting, and postprandial pain were shown to be reduced from 93% to 50%, 79% to 30%, and 58% to 30%, respectively ($P < .05$); however, chronic pain, diarrhea, and dumping syndrome were not significantly affected.

Subtotal gastrectomy involves resection of approximately 70% of the stomach including the antrum and pylorus, with closure of the duodenum and reestablishment of continuity with a Roux-en-Y jejunal segment. Watkins et al reported the largest longitudinal experience with subtotal gastrectomy in diabetic patients with gastric atony. They demonstrated that 6 of 7 patients had immediate resolution of vomiting symptoms and improvement in quality of life, which persisted up to 6 years postoperatively. Zehetner et al compared 2 groups treated with GES, laparoscopic subtotal gastrectomy, or a
combination of the 2 if GES failed. Thirty-one patients received laparoscopic subtotal gastrectomy, whereas 72 received GES. Evaluation demonstrated that 30-day morbidity was significantly greater in the gastrectomy group than the GES group (23% vs 8%), but this difference decreased over time. Although two-thirds (63%) of the GES group attained symptom improvement, 87% of those in the gastrectomy group reported significant improvement in nausea, vomiting, and epigastric pain. Nineteen (26%) of the GES group had to have the device removed because of device malfunction, infection, or failure to respond. These patients received laparoscopic subtotal gastrectomies, with 100% reported symptom improvement. This success with laparoscopic gastrectomy prompted Lipham and colleagues to propose this approach as first-line therapy for the surgical treatment of gastric atony.

Recent observations of increased gastric emptying in bariatric surgical patients have prompted multiple case reports and case series describing the use of longitudinal sleeve gastrectomy for the treatment of patients with atony. Sleeve gastrectomy involves removal of the body and fundus of the stomach and stapling along the lesser curvature to create a tubular stomach. Bagloo and colleagues reported an initial case series of sleeve gastrectomy in 4 patients with diabetes with atony. Three of the 4 patients had resolution of their symptoms after a minimum follow-up of 6 months. Similarly, Meyer and colleagues demonstrated, in 9 morbidly obese patients with diabetes and gastroparesis, that laparoscopic sleeve gastrectomy resulted in the resolution of gastroparesis symptoms and improved gastric emptying studies. The introduction of laparoscopic gastric resection with reconstruction has allowed for decreased morbidity in populations with complex diabetic histories prone to complications and morbidity secondary to chronic malnutrition.

McCallum and colleagues reported their experience on 8 patients with gastroparesis who underwent completion gastrectomy after failing to respond to both available and experimental medical therapies with prokinetic agents. They concluded that although completion gastrectomy is a radical approach, it can provide reliable relief of symptoms in a select group of patients with chronic refractory gastroparesis after partial gastric resection for gastric outlet obstruction secondary to peptic ulcer disease. Subsequently, these authors reported on their own experience at a GI motility referral center. They reported on 9 of 200 patients (4.5%) who received GES for gastric atony who then underwent a total gastrectomy with placement of a jejunostomy tube as a
last resort to control their symptoms. Nausea and vomiting improved by an average of 55%; all patients became nutritionally stable, previously placed jejunostomy tubes were able to be removed, and the quality of life was such that they all would recommend the procedure. Furthermore, all patients had a significant reduction in the number of emergency room visits and hospitalizations.

OUTCOMES

Natural History

In the Olmsted County epidemiology study,\(^3^9\) one-third of all patients with incident gastric atony died, and another one-third required hospitalization, medications, or tube feeding related to atony. Furthermore, overall survival in patients with gastroparesis was significantly lower than that of the Minnesota white population, reiterating the vast impact it can have on patient morbidity and mortality.

Impact on Quality of Life

As stated earlier, the impact of gastroparesis on quality of life can be severe and debilitating. Although nausea and vomiting are the cardinal symptoms of gastroparesis, data from the NIDDK Gastroparesis Clinical Research Consortium suggested that upper abdominal pain or discomfort is not uncommon and is often severe.\(^{185}\) Moderate to severe pain was associated with more severely delayed gastric emptying, worse quality of life, depression, and anxiety.\(^{185}\) Moreover, among patients with moderate to severe pain, 48% were chronically taking opiates. To what extent this impact is related to GI symptoms per se versus comorbid conditions (eg, depression) and/or medications (eg, opiates) is unclear.

Data on the impact of GI symptoms on quality of life among patients with gastric atony in the community are limited. Among a community cohort of people with T2DM, the physical and mental quality of life as assessed by the Short Form-36 were lower in patients with diabetes with GI symptoms compared with population norms.\(^{186}\) The quality-of-life scores in all
subscales decreased markedly with increasing numbers of distinct GI
symptoms, and the association between GI symptoms and poorer quality of
life in DM was independent of age, sex, smoking, alcohol use, and type of
DM.\textsuperscript{186}

Race has also been shown to be associated with the impact of GI
symptoms on quality of life in patients with DM. One study reported that
nonwhite patients with gastroparesis had more severe symptoms, poorer
quality of life, and used more health care resources than white patients.\textsuperscript{187}
The 2 groups differed in health care use, with 49\% of nonwhite patients
reporting more than 4 gastroparesis-related emergency department visits and
42\% reporting more than 4 gastroparesis-related hospitalizations, compared
with 20\% and 14\% of white patients, respectively. In this study, nonwhite
race, sex, age, and age of onset were independently associated with symptom
scores, whereas the causes of gastroparesis and GE times were not. High
unemployment rates, lower household income, and work absenteeism are also
variably associated with gastroparesis.\textsuperscript{96,150}

\textbf{Mortality Rates}

Overall survival in patients with idiopathic gastroparesis was significantly
lower than the age- and sex-specific expected survival computed from the
Minnesota white population.\textsuperscript{39} A review of several case series observed that
the mortality rates in patients with gastroparesis range from 4\% and 38\%.\textsuperscript{188}
The best outcomes were observed in a largely outpatient-based group of
patients followed for approximately 2 years, and the highest death rates were
reported in patients with diabetes with gastroparesis requiring nutritional
support.\textsuperscript{30,189-192} In a study of 86 patients with diabetes, approximately 25\%
had died during follow-up of at least 9 years, but gastroparesis was not
associated with mortality after adjustment for other disorders.\textsuperscript{193} However,
this study did not ascertain the relationship between diabetic gastroparesis
and other medical conditions. Whether this increased mortality is driven by
gastroparesis is unknown. Data on long-term natural history in the
community are lacking.

\textbf{FUTURE DIRECTIONS}
Chronic disturbances of GI function encompass a wide spectrum of clinical disorders that range from common conditions with mild-to-moderate symptoms to rare diseases characterized by a severe impairment of digestive function, chronic pain, vomiting, bloating, and severe constipation. Patients at the clinically severe end of the spectrum such as those with gastric atony can specifically experience profound changes in gut transit and motility. In a subset of these patients, histopathologic analyses have revealed abnormalities of the gut innervation, including the ENS, termed enteric neuropathies, and offer a possible future direction of study to increase our arsenal of treatment targets. At the other end of the spectrum, medical treatment options continue to be first-line therapy for those with “manageable” symptoms. Nevertheless, acquisition of knowledge regarding this disease can hopefully enable the future development of novel targeted therapeutic approaches to help relieve the symptomatic and emotional burden of those afflicted.

CONCLUSION

Gastric atony continues to be a medical problem with significant effects. The causes are multifactorial and may have mild to severe symptoms. Acquisition of consistent cure rates will undoubtedly require early diagnosis, prompt workup, and more effective, yet minimally invasive medical treatment options.

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INTRODUCTION

Tumors of the stomach are diverse in presentation, symptoms, and prognosis. In this chapter, the authors will first describe the epidemiology, presentation, and management of gastric adenocarcinoma. Subsequently, gastric polyps, mesenchymal tumors (eg, gastrointestinal [GI] stromal tumors), and the rare gastric sarcoma and lymphoma will be discussed.

GASTRIC ADENOCARCINOMA

Historic Background

The first description of stomach cancer documented in Western literature is generally thought to be that of Avicenna (980-1037). Many years later, in
1761, Morgani published a manuscript on malignancies of the stomach. In 1879, Pean was believed to perform the first gastric resection for cancer, followed by Billroth performing the first described pyloric resection in 1881, and Schlatter successfully performing the first total gastrectomy (TG) in 1897. In 1951, McNeer et al recommended a more extensive resection for cancer, including TG with distal pancreatectomy and splenectomy.¹

Incidence and Pathology

While gastric cancer (GC) is the third leading cause of cancer-related death worldwide, significant differences in its incidence exist across the continents.² Specifically, a higher incidence is found in Japan and Eastern Asia (approximately 18-25 cases/100,000) than in Europe and North America (approximately 8-10 cases/100,000).³ The incidence of GC in the United States is low as it is currently the 15th most prevalent cancer. In 2015, 24,500 patients were diagnosed with GC, and nearly 10,000 persons are projected to die from GC in 2016. The estimated overall 5-year survival approaches 30%.⁴

Gastric cancer is a malignant solid organ tumor of older adults (>65 years). The median age of diagnosis is 69 years of age. Similar to other solid organ cancers, older adults are primarily affected.⁵ In recent years, the incidence of GC has been rising in younger adults (age <50 years). Initially, their outcomes were mistakenly perceived to be worse than older adults. However, a recent large population-based study showed that younger patients were more likely to present with advanced or metastatic disease; however, they have a more favorable stage for stage prognosis than their older counterparts.⁶

In addition to age, race and ethnicity also impact the presentation, treatment, and prognosis of GC. In the United States, Caucasians typically present with proximal GC, often involving the gastroesophageal junction (GEJ), whereas Asians tend to present with early stage disease, distal tumors, and have a more favorable prognosis. In contrast, African Americans and Hispanics are more likely to present with advanced stage disease and harbor worse outcomes, likely due to a combination of issues related to access to care and multiple morbidities.⁷,⁸
Gastric Cancer Risk Factors

The development of GC has been attributed to several risk factors. The most significant appears to be an infection with *Helicobacter pylori*. This is particularly an issue in developing countries and is more often observed in GC outside the cardia, as supported by a robust meta-analysis of 42 observational studies. Diets that contain salt, smoked or poorly preserved foods, nitrates, nitrites, and secondary amines have been shown to contribute to development. In contrast, diets that are rich in raw vegetables, fresh fruits, vitamin C, vitamin A, calcium, and antioxidants have been found to be protective. Cigarette smoking is another major environmental risk factor with 2- to 3-fold increased risk for GC. Excessive alcohol consumption may also pose an increase. Finally, GC is associated with a wide host of hereditary GC syndromes outlined below.

HEREDITARY GASTRIC CANCER SYNDROMES

Ten percent of GCs concentrate in families, and less than 3% are due to an inherited cancer syndromes. In evaluating these patients, close attention should be paid to the family history along with the pathology to uncover those with hereditary GC. Features suggestive of hereditary risk include GC in two or more first-degree relatives and/or second-degree relatives, cancers in multiple generations, signet ring cell histology, and early age of onset (<45 years).

Hereditary diffuse gastric cancer (HDGC) was the first hereditary GC to be identified. HDGC is caused by germline mutations in *CDH1*, the gene that encodes the E-cadherin protein. The average age of onset for HDGC is 38 years (range 14-69 years); premenopausal lobular breast cancer can occur as well. By the age of 80 years, 70% of men and 56% of women with HDGC developed diffuse gastric cancer (DGC); lobular breast cancer develops in 42% of women.

To better manage these risks, the International Gastric Cancer Linkage Consortium has proposed criteria for HDGC. Germline *CDH1* testing is recommended in three groups: (1) families with two or more patients with GC at any age and one confirmed DGC, (2) individuals with DGC before the age of 40, and (3) families with diagnoses of both DGC and lobular breast
cancer (one diagnosis before the age of 50). CDH1 testing should also be considered in the following three groups: (1) patients with bilateral lobular breast cancer or a family history of two or more cases of lobular breast cancer occurring before the age of 50, (2) patients with a personal or family history of cleft lip/palate and DGC, and (3) tumors with in situ signet ring cells and/or the pagetoid spread of signet ring cells.

In addition to the early age of onset, one of the key challenges when families with HDGC is the relative ineffectiveness of endoscopic surveillance in detecting DGC alone. In this regard, TG for DGC patients and prophylactic gastrectomy (for at-risk family members) is appropriate for CDH1 carriers. These recommendations are less clear in managing families who meet established criteria but in whom no mutation is present.

Other different hereditary cancer syndromes with increased risk of GC include Lynch syndrome, Li-Fraumeni syndrome, familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome, MUTYH-associated polyposis, hereditary breast, and ovarian cancer syndrome. As such, it is imperative to refer at-risk patients and their families to cancer genetics professional to discuss options for management.

**Prognostic Factors and Surgical Outcomes**

**OVERALL SURVIVAL OUTCOMES**

In western populations, patients predominantly present with advanced stage disease and an overall 5-year survival rate of less than 30%. Nearly 65% of GC patients, collected in the US National Cancer Database, are found to have advanced disease (T3/T4). Indeed, up to 85% of these patients harbor nodal metastases at the time of diagnosis. The median survival in persons who undergo curative gastrectomy is 24 months (5-year survival 20%-30%). However, when palliative or no GC therapy is performed, these median survival rates drop to 8 and 5.4 months, respectively.

In this current era of personalized cancer medicine, the prognosis after R0-gastric cancer resection has been examined across several externally validated and electronically available patient-centered nomograms. The nomograms go beyond elements of the current American Joint Committee on Cancer (AJCC) staging system to also account for the patients’ age, sex, tumor location, tumor size, negative/positive lymph node status, and
pathologic features/classification of the tumor(s).\textsuperscript{20,21}

**GASTRIC CANCER SURGERY OUTCOMES**

Due to regionalizing complex surgical care, including major cancer surgery, mortality rates after gastrectomy (namely TG) have become relatively very low (<2%). A high hospital volume with at least 11 gastrectomies per year is predicted to have a 3% to 6% lower in-hospital mortality than lower volume centers.\textsuperscript{22,23}

While postgastrectomy mortality rates are low, the postoperative morbidity rate remains high, approaching 40%.\textsuperscript{24} These complications include systemic (pulmonary embolism, pneumonia, myocardial infarction, deep vein thrombosis) and technically-related issues (anastomotic leak, anastomotic stricture).

Postgastrectomy readmission rates are estimated to range from 7% to 20%. These readmissions are largely driven by operative GI complications. It was noted that within this subset of patients, those with a higher preoperative nutritional risk and postoperative infections were found to be at the highest risk of complications requiring readmission.\textsuperscript{25,26}

**PATHOLOGIC STAGING**

The pathologic staging is a T-, N-, M-based AJCC staging system (Table 31-1).

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<th>PATHOLOGIC STAGING</th>
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<td>The pathologic staging is a T-, N-, M-based AJCC staging system (Table 31-1).</td>
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**TABLE 31-1: AJCC 8TH EDITION TNM STAGING FOR GASTRIC ADENOCARCINOMA**
CLINICAL MANIFESTATIONS

Gastric cancers can present with specific or nonspecific GI symptoms.
Specific symptoms include early satiety, dysphagia, or weight loss, often prompting the treating caregiver to request an upper endoscopy for diagnosis and further workup. However, when patients present with nonspecific symptoms that are easily mistaken for benign conditions (eg, gastroesophageal reflux, peptic ulcer disease), the diagnostic process can be considerably delayed. Indeed, the relatively low incidence rates and lack of cost effective screening program for GC in the United States only add to the difficulty of diagnosing these patients early. Patients with advanced disease can present with a palpable abdominal mass, cachexia, ascites, or bowel obstruction.

The cardinal physical examination findings of metastatic disease, such as an enlarged supraclavicular node (Virchow node) or a drop metastasis in the pouch of Douglas (Blumer shelf), are typically rare. Overall, most physical examination findings are unfortunately found to be nonspecific and unreliable in making a definitive diagnosis.

**Pretherapy Workup**

**HISTORY AND PHYSICAL EXAMINATION**

The workup should start with a thorough history and physical examination. Specific questions in the history should include whether the patient has experienced unintentional weight loss, anorexia, early satiety, vomiting, bleeding, epigastric burning, pain, or discomfort. The surgeon should also ask about social factors, such as tobacco and alcohol use, and the consumption of large amounts of nitrate-rich or smoked/preserved foods. A previous history of *H. pylori* infection or a family history of GC are also important considerations. Finally, assessing the patients’ performance status and frailty are also critical to predict their ability to tolerance GC therapies.

**LABORATORY WORKUP**

In addition to a thorough history and physical examination, the pretherapy evaluation in patients with GC should include:

- Complete blood count (CBC): To evaluate and treat GC- or treatment-related anemia
• Basic metabolic panel (BMP): To detect electrolyte abnormalities, especially in gastric outlet obstruction, and to detect renal functional abnormalities prior to receiving contrast-enhanced imaging and/or preoperative systemic therapy
• Liver function panel: To check prior to the induction of preoperative systemic therapy
• Albumin and prealbumin: To uncover malnutrition especially since approximately 30% to 80% of patients diagnosed with GC are malnourished.

Genetic Testing for Hereditary Gastric Cancer. As previously described, the operating surgeon should be aware of potential features in the history or pathology report that are suggestive of hereditary GC. As part of the multidisciplinary approach to GC, a referral to a professional cancer genetic counselor is imperative to better manage this unique cohort of patients and their families with potential hereditary GC.

In family carriers of the CDH1 mutation, a shared decision is made around prophylactic TG. Furthermore, support from a social worker and a psychologist should be available to address and manage the burden of dealing with such major life-changing treatment decisions.

Diagnostic and Staging Modalities

SCREENING FOR GASTRIC CANCER (EAST VS WEST)

Unlike the United States and Europe, screening esophagastroduodenoscopy (EGD) is typically performed in countries with a high prevalence of GC, such as Japan and South Korea. The overall goal is to improve overall outcomes. However, in regions outside of Asia with a lower prevalence, endoscopic screening has not been shown to be beneficial for primary prevention in the general population.

As previously discussed in other parts of this chapter, screening should be considered in certain cases of hereditary GC syndromes. For example, in persons with adenomatous polyposis syndromes (eg, FAP), screening EGD is recommended starting at age 25 to 30 years and repeated every 0.5 to 4 years based on the Spigelman stage of duodenal polyposis. In cases of HDGC, prophylactic TG is the recommended approach at a young age, obviating the
need for screening EGD and potentially preventing the development of GC.

**Endoscopy and Endoscopic Ultrasound for Gastric Cancer.** Upper GI endoscopy plays a key role in establishing the diagnosis and in treatment planning of GC. However, upper endoscopy lacks standardized quality measures for adequate endoscopy similar to colonoscopy for colonic polyps or cancer (eg, caecal intubation, time for completions). As such, surgeons and their GI counterparts need to work collaboratively to identify key GC-relevant elements including: (1) the exact location of the cancer within the stomach to determine the extent of gastrectomy, (2) the relation of the cancer to the esophagus to ascertain the need for distal esophageal resection, and (3) the presence of linitis plastica as a marker of systemic disease pointing toward the need for preoperative systemic therapy.

Experienced endoscopists can leverage several other techniques to assist with identifying high-risk lesions using magnifying endoscopy, chromoendoscopy, narrow band imaging, flexible spectral color enhancement endoscopy (FICE), and confocal laser endomicroscopy (CLE). These techniques have shown promise in improving the endoscopic detection of worrisome lesions and in guiding biopsy site selection.\(^\text{30}\)

Endoscopy also represents an opportunity for tissue collection and molecular profiling (eg, Her2neu) for advanced and progressive GC for possible enrollment in emerging GC immune therapy trials (eg, tissue for PD1 status). When preoperative systemic therapy is employed, this diagnostic tool can also provide useful treatment and prognostic information, such as the status of the response to preoperative therapy or distal esophageal involvement.

Nearly 10% of gastric patients diagnosed before the age of 50 years also have synchronous colon cancer, and a preoperative screening colonoscopy should be performed on all these patients.\(^\text{31}\)

Endoscopic ultrasound (EUS) has also emerged as an accurate staging tool in GC to compliment high-resolution cross-sectional imaging and staging laparoscopy.\(^\text{32,33}\) By placing the EUS probe directly over the primary tumor, EUS can distinguish T1 (early GC) from T2 (invasion of muscularis propria) lesions with a sensitivity of 85% and a specificity of 90%. Additionally, the distinction between T1 and T2 (superficial) versus T3 and T4 (advanced) lesions can be achieved with a sensitivity of 86% and a specificity of 90%.\(^\text{34}\)
N-staging is also important. EUS is used to confirm the presence of nodal involvement with a sensitivity of 83% and a specificity of 67%. Nodal areas of particular interest include the paracardial, superior gastric, inferior gastric, and pancreaticiolienal regions. EUS is highly operator-dependent and provides accurate loco-regional staging of gastric adenocarcinoma that can inform decisions regarding preoperative systemic therapy versus surgery-first followed by adjuvant therapy.

**Contrast-Enhanced Cross-Sectional Imaging.** In addition to EUS, high-resolution multidetector computed tomography (CT) is the preferred imaging modality for the staging and post-treatment surveillance of gastric adenocarcinoma. Because of its thin slices and multiplanar capabilities, this modality provides accurate visualization of the primary tumor and surveys the chest, abdomen, and pelvis for metastatic disease.

At our institution (MedStar Georgetown University Hospital), we developed a gastric tumor protocol CT for patients with suspected or known gastric masses; the stomach is distended with oral contrast material or water prior to performing the CT. Distention of the stomach helps differentiate a collapsed gastric wall from tumor. It has been shown that the combination of focal or eccentric wall thickening greater than 1 cm and intravenous contrast enhancement is highly specific. This gastric tumor protocol CT is extremely useful when considering the laparoscopic resection of other gastric neoplasms, such as gastric GI stromal tumors or neuroendocrine tumors. Further details are found in other parts of this chapter. We also recommend taking advantage of the coronal and sagittal reconstructions, which display helpful gastric anatomy and, in some cases, the optimal planes for visualizing tumors with adjacent organ involvement.

Overall, the accuracy of CT for staging is estimated to range from 66% to 93%. The limitations of CT are its inability to detect subtle serosal invasion, metastatic disease in normal-sized lymph nodes, and small peritoneal deposits that may be below the resolution of CT. Hence, our strong preference is to also add staging laparoscopy to overcome these known limitations.

Positron emission tomography (PET) with 2-deoxy-w-\(^{(18)}\)fluoro-D-glucose (FDG PET) combined with CT (FDG PET CT) is valuable in some patients for the detection of occult disease. However, it lacks accuracy in mucinous or diffuse disease, such as linitis plastica.
DIAGNOSTIC LAPAROSCOPY AND PERITONEAL CYTOLOGY

Diagnostic laparoscopy (DL) is highly recommended as an additional staging tool. DL was found to upstage 20% to 25% of patients and thus can prevent nontherapeutic laparotomies in patients with subradiographic or occult hepatic or peritoneal metastasis. The risk of peritoneal disease is much higher in those with linitis plastica and AJCC stage T3+, N+ disease; DL can inform the treatment strategy of a patient with suspected stage IV disease. DL can also be utilized to re-evaluate disease response to systemic therapy, to obtain peritoneal cytology, or to place a preoperative feeding tube.

The use of peritoneal cytology continues to be an area of controversy. Peritoneal cytology that is positive for tumor cells has been shown to be a poor prognostic marker in the absence of visible tumor spread (C1 disease). The estimated median survival in patients with C1 disease was only 20 months. At our institution, we employ a selective approach for peritoneal cytology in the following situations: (1) linitis plastica, (2) borderline performance status, or (3) evidence of AJCC T4 disease on imaging.

In summary, our multidisciplinary staging approach is to employ the following three tools: (1) EUS performed by an experienced gastroenterologist, (2) high-resolution CT of the chest, abdomen, and pelvis, and (3) staging laparoscopy with or without cytology.

Multidisciplinary Treatment Strategy for Operable Gastric Cancer

A multidisciplinary treatment strategy is crucial in patients newly diagnosed with GC. We recommend a stage-dependent treatment approach informed by the three patient-centered aspects:

1. The patient’s suitability to undergo curative gastrectomy
2. Accurate three-tool pretherapy staging
3. Sequence of GC therapy (surgery-first vs perioperative therapy)

SUITABILITY TO UNDERGO CURATIVE
GASTRECTOMY

The operating surgeon should consider several important preoperative variables prior to undertaking surgical therapy. Evaluating the underlying comorbidities and performance status are key preoperative considerations. Managing the burden of existing comorbidities is also important to enhance operative recovery after gastrectomy. As previously mentioned, reversing preoperative malnutrition and electrolyte abnormalities will lead to better operative outcomes. In some regards, improving some factors, such as frailty or performance status, may not be an achievable goal. However, a preoperative rehabilitation stay prior to surgical treatment may reduce the impact of frailty on operative outcomes.42,43

ACCURATE THREE-TOOL PRETHERAPY STAGING

Up to 30% of newly diagnosed GC patients harbor occult radiographic metastases. As such, we recommend accurate stage-dependent treatment using a combination of EUS, high-resolution contrast-enhanced cross-sectional imaging, and DL. Together, patients can avoid the pitfalls of nontherapeutic laparotomy for GC.

SEQUENCE OF GASTRIC CANCER THERAPY (SURGERY-FIRST VERSUS PERIOPERATIVE THERAPY)

Margin-negative (R0) gastrectomy and adequate lymphadenectomy together represent the pillars of surgical therapy for operable GC. Level I evidence continues to strongly support a multimodal approach in persons with GC to enhance their overall and disease-free survival. In this regard, most patients with AJCC T2+ or N+ operable GC are offered one of the following two treatment sequences: (1) surgery-first, followed by adjuvant chemotherapy and/or chemoradiotherapy, or (2) perioperative systemic therapy. The latter is gaining more traction in Europe in light of emerging evidence that shifts the operable GC treatment paradigm to that of a perioperative approach. Additional details will be provided in parts of the current chapter.

At our institution, we take patient- and tumor-related factors into consideration to guide the sequence of therapy. Factors such as the presence of linitis plastica and the tumor location are considered during the treatment
strategy planning. For example, a proximal GC location, the presence of linitis plastica, or borderline performance status all favor perioperative therapy. In those with proximal GC, prolonged operative recovery and higher operative complication rates are to be expected after TG; hence the rationale for perioperative therapy. In contrast, factors including an early stage GC or distal GCs (and their subsequent tumor-related complications, including bleeding or obstruction) favor a surgery-first approach.

**Surgical Approaches for Operable Gastric Cancer**

**TOTAL GASTRECTOMY**

Total gastrectomy is typically performed in patients with proximal GCs (cancers of the cardia or fundus). This operation entails the extirpation of the entire stomach, GEJ, and omentum, with subsequent restoration of intestinal continuity using a Roux-en-Y reconstruction (Figs 31-1 A and B). The stomach is carefully dissected and mobilized free of all attachments. The arterial supply of the stomach is then ligated at its origin, followed by the removal of the stomach. TG is considered complete when normal esophageal and duodenal mucosa is included in the margins.\(^{11,44}\)
FIGURE 31-1A Subtotal gastrectomy with D2 lymphadenectomy for gastric adenocarcinoma with pathology demonstrating pT4a, pN3b, 24/44 lymph nodes positive.
FIGURE 31-1B Roux-en-y reconstruction after total gastrectomy.
SUBTOTAL GASTRECTOMY

A subtotal gastrectomy (STG) is recommended for patients with midbody or distal GCs (Fig. 31-2). Unlike TG, STG entails the removal of 70% to 80% of the stomach. Adequate negative resection margins (ie, 4-6 cm proximal and 2 cm distal margins) are necessary to ensure an appropriate oncologic resection. In line with TG, it is imperative to ligate the gastric arteries at their origins, with the exception of the short gastric vessels; these should be maintained to prevent remnant ischemia. Gastrointestinal continuity is restored either via a Roux-en-Y gastrojejunal reconstruction (our preference) or a loop gastrojejunostomy. The rationale behind the use of a Roux-en-Y gastrojejunal reconstruction instead of a loop gastrojejunostomy is to avoid bile reflux into the gastric remnant. Hand-sewn or a stapled anastomosis is considered safe and appropriate.
Equivalent overall and disease-free survival have been noted after TG versus STG for distal GC (overall 5-year survival rate of 62.4% vs 65.3% for TG vs STG, respectively).\textsuperscript{22} When compared to TG, STG has been shown to provide more favorable nutritional outcomes and quality-of-life.\textsuperscript{45}

**Extent of Lymphadenectomy for Gastric Cancer**

While adequate lymphadenectomy with histopathological nodal evaluation are important components of GC staging and therapy, the extent of lymphadenectomy has been an area of significant debate and controversy.\textsuperscript{46} The classification of lymphadenectomy for operable GC falls into two categories: (1) the topographic location of the lymph node stations and (2) the extent of nodal removal, extending away from the stomach. The Japanese Research Society for Gastric Cancer has described the topographic classification of histopathological and nodal evaluations. This classification is based on nodal stations within various parts of the stomach and its arterial supply, and extends to the para-aortic nodal region.\textsuperscript{47,48} The second classification is based on the extent of nodal removal and is also known using the “D” nomenclature. As such, four tiers of lymphadenectomy exist: (1) D0 denotes incomplete removal and therefore is considered an inadequate nodal dissection, unless palliative gastric resection is considered; (2) D1 entails the removal of the perigastric lymph nodes; (3) D2 is D1 combined with the removal of the nodal stations around the celiac trunk, along with a distal pancreatectomy and splenectomy; and (4) D3 includes D2 + resection of the nodes from the celiac axis to the inferior mesenteric artery.\textsuperscript{48}

The evaluation of lymphadenectomy for GC has progressed in Europe. Initially, two large European trials from the United Kingdom and Netherlands demonstrated no survival differences between D1 versus D2 lymphadenectomy (Fig. 31-3). In both trials, enrollees suffered worse operative outcomes after D2 lymphadenectomy.\textsuperscript{49–51} However, the long-term results from the Dutch Gastric Cancer Group trial demonstrated a more favorable survival benefit for D2 nodal dissection. Specifically, the 15-year overall survival (OS) rates were 21% and 29%, respectively, for the D1 and D2 groups ($P = 0.34$). Lower rates of local (12% vs 22%) and regional
recurrence (13% vs 19%) were also associated with D2 lymph node dissection. Contemporary European studies are currently evaluating survival benefits with D2 compared to D1 lymphadenectomy in the setting of improved D2 operative outcomes.  

Figure 31-3  D1 versus D2 Lymphadenectomy. D1 lymphadenectomy is resection of perigastric lymph nodes (brown nodes). D2 lymphadenectomy is an extended resection of nodes surrounding celiac artery area (green nodes) with splenectomy and distal pancreatectomy (not shown).

To better answer this question of survival benefit of D2 lymphadenectomy in the Asian population where GC is more prevalent, JCOG9501 was a Japanese randomized controlled trial conducted to compare D2 dissection alone versus D2 with para-aortic nodal dissection (PAND) for operable T2b–T4 GC (T2b, T3, or T4). D2 nodal dissection with PAND did not improve the overall and relapse-free survival rates compared to D2 dissection alone (5-year OS rates were 70.3% and 69.2%, respectively). Recent meta-analyses of D1 versus D2 trials have demonstrated that D2 dissection is associated with a significantly higher postoperative risk, but with equivalent
long-term survival rates between D1 versus D2 lymphadenectomy.\textsuperscript{59,60}

A Cochrane review meta-analysis of over 2500 patients enrolled in eight Asian and European lymphadenectomy (D1, D2, or D3) GC trials showed no difference in survival between D2 and D3 even in Asian lymphadenectomy trials. Furthermore, no significant differences were found in the overall and disease-free survival in trials of D1 versus D2 lymphadenectomy. However, D2 lymphadenectomy was associated with a significantly improved disease-specific survival rate compared to D1, albeit with two higher operative mortality rates.\textsuperscript{61,62}

The differences in Asian versus western results are perhaps attributable to differences in disease biology, surgical expertise, variations in where GC surgery is performed (especially in the United States), and differences in BMI in Eastern versus Western GC patients.\textsuperscript{51,63}

In light of this mixed level of evidence, most current western guidelines recommend at least a D1 lymphadenectomy with a total nodal yield of 15 or more lymph nodes. A modified D2 (also known as pancreas and spleen-preserving D2 lymphadenectomy) remains an approach in expert centers.

**Minimally Invasive Gastrectomy for Gastric Cancer**

In addition to open GC surgery, minimally invasive gastrectomy (MIG) has emerged as an investigational surgical therapy. Nonrandomized and observation studies, using propensity score case-matching, have shown that MIG is associated with reductions in surgical site pain, the length of hospital stay, the use of narcotics, and postgastrectomy complication rates.\textsuperscript{64,65} In a small prospective randomized investigation of laparoscopic versus open STG, operative mortality rates (3.3\% vs 6.7\%, respectively), 5-year OS (58.9\% vs 55.7\%, respectively), and disease-free survival rates (57.3\% vs 54.8\%, respectively) were more favorable for MIG, although the difference was not statistically significant.\textsuperscript{66,67}

While emerging investigations point toward improved outcomes with MIG in operable GC, several studies have included subjects with smaller tumor sizes or early-stage GC. This observation should be factored into comparisons of MIG with open GC surgery in western populations that typically have larger tumor sizes and more advanced disease.
There are two ongoing large prospective randomized MIG versus open gastrectomy trials in Asia. The first is a multihospital phase III Japanese study to assess the OS of laparoscope-assisted distal gastrectomy compared to open distal gastrectomy in patients with early-stage GC.\textsuperscript{68} Klass 01 is another ongoing large Korean prospective randomized trial of laparoscopic versus open gastrectomy for distal GC.\textsuperscript{69}

To date, MIG for GC in the United States remains in its infancy and will require additional larger randomized clinical trials for more adoption among the surgical community in the United States.

**SYSTEMIC CHEMOTHERAPY**

Multimodality therapy for GC is designed to provide patients and their family with better care by prolonging the survival outcomes, reducing the risk of recurrence along with minimizing the burden of the disease. In this regard, the benefit of integrating surgical therapy (gastrectomy and lymphadenectomy) with systemic therapy has been demonstrated to reduce the recurrence risk of GC following surgical resection. In one meta-analysis, the use of any form of chemotherapy as adjuvant therapy to surgical resection for GC produced an 18% overall reduction in the risk of cancer recurrence.\textsuperscript{70} Currently postoperative chemotherapy and radiation therapy is being compared to the perioperative use of chemotherapy alone.

**Adjuvant Chemotherapy and Radiation Therapy.** In 2001, the US Intergroup trial (INT-0116) established the combination of chemotherapy with radiation therapy as one possible adjuvant care standard for operable GC. In this randomized, phase III, open-label trial, patients were eligible for enrollment if their tumor was stage Ib to stage IVM0; patients were assigned to the treatment arm (5-fluorouracil and leucovorin, concurrent with radiation) versus surgery alone.\textsuperscript{71} In the adjuvant chemotherapy and radiotherapy arm, OS was statistically better (36 months), in comparison to the control arm (27 months, \( P = 0.005 \)).

In the Intergroup trial, only 64% of patients assigned to the treatment arm were able to complete therapy, underscoring the toxicity of adjuvant therapy especially in the context of the morbidity and operative recovery associated with the necessary surgical therapy. In addition, 77% of enrolled patients had a distal tumor location within the stomach. While specific histologic subtypes
were not reported, a distal location is typically associated with the less aggressive intestinal histology of gastric adenocarcinoma. Thus, the tumor location and biology could explain some of the benefit of this adjuvant approach. Finally, this trial was also notable for the lack of adequate nodal evaluation in as many as 50% of trial participants, thus raising questions about whether adjuvant therapy compensated for inadequate GC surgery or unrecognized node-positive disease.

**Perioperative Chemotherapy.** In 2006, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial in the United Kingdom established an alternative approach to adjuvant therapy for resectable GC through the use of perioperative chemotherapy alone. This phase III, open-label study randomized patients deemed to have resectable GC to either six cycles of chemotherapy (three each, presurgery and postsurgery) or to surgery alone. Patients with nonmetastatic gastric adenocarcinoma of stage II or higher were eligible. Unlike the Intergroup trial, chemotherapy in the MAGIC trial consisted of a triple regimen of epirubicin, cisplatin, and 5-fluorouracil. Modifications to this regimen, using oxaliplatin instead of cisplatin, and capecitabine instead of 5-fluorouracil, have been shown by the Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) study to be acceptable, affording similar outcomes but with reduced toxicity.

In the MAGIC trial, the use of perioperative chemotherapy was associated with a significant survival benefit versus surgery alone (5-year survival rates of 36% and 23%, respectively; \( P = 0.009 \)). As in the case with the Intergroup trial, several characteristics of the MAGIC trial need to be highlighted. First, while 90% of patients assigned to the treatment arm were able to complete the preoperative cycles of chemotherapy, only 57% began the postoperative chemotherapy cycles and only 43% completed them. While again highlighting the challenge of adjuvant therapy postoperatively, the relatively consistent ability of patients to tolerate neoadjuvant therapy is also noted. Second, the majority of tumors were located proximally, including 15% that were at the GEJ and 11% that were in the distal esophagus. While the histologic subtypes were not reported in the MAGIC trial either, the more aggressive diffuse subtype tends to predominate in this proximal tumor location. Together, these data suggest that the perioperative approach to adjuvant therapy could be optimal for a proximal tumor location and
histology.

**Treatment Recommendations.** Because of the difficulties in directly comparing the MAGIC and Intergroup trials to inform the sequence of GC therapy, the adjuvant chemotherapy or chemoradiotherapy in resectable gastric cancer (CRITICS) trial was conducted in Europe. In the CRITICS trial, all patients received neoadjuvant chemotherapy (consisting of three cycles of epirubicin, cisplatin or oxaliplatin, and capecitabine) followed by adequate surgical therapy (gastrectomy and lymphadenectomy). After surgery, patients randomly received either an additional three cycles of the same chemotherapy or concurrent chemotherapy and radiation therapy (45 Gy combined with cisplatin and capecitabine). While the analysis is ongoing, preliminary results presented in 2016 suggest that there is no significant difference in OS between these two postoperative adjuvant approaches. It is important to recognize that these results cannot be generalized into one approach, and that the selection decisions must consider the individual characteristics of the patient’s tumor. As previously described, in patients with a proximally located, diffuse-histologic subtype of cancer, perioperative chemotherapy akin to the MAGIC and CRITICS approach should generally be recommended. Moreover, given the observed effect of operative recovery on tolerance of adjuvant therapy, preoperative chemotherapy is perhaps an attractive approach in those with an advanced tumor stage (T3/T4 or any node-positive). Conversely, in those with a distally located, intestinal-histologic subtype of cancer, postoperative chemotherapy and radiation therapy akin to the Intergroup trial is more appropriate. Additionally, those patients whose symptoms would not allow for surgical delay while neoadjuvant chemotherapy is administered (eg, tumor-related bleeding or obstruction that cannot be relieved by other methods) should generally proceed directly to surgery. The interplay of these different factors underscores the need for a multidisciplinary consultation to establish the treatment sequence and adjuvant plans prior to any therapeutic intervention.

**RADIATION THERAPY FOR OPERABLE GASTRIC CANCER**

Local and regional failure after surgical therapy for operable GC is relatively common and detrimental to patients’ quality of life. In the aftermath of
gastrectomy, several retrospective studies have shown that 40% of patients will develop a recurrence and in nearly 26% recurrence is local-regional alone.\textsuperscript{77,78} These failures have stimulated investigation into integrate radiotherapy with surgery along with systemic therapy.

As previously described, the INT-0116 trial remains one of the largest randomized studies in the United States to evaluate the role of adjuvant chemoradiation.\textsuperscript{71,79} The updated results of 10-year follow-up demonstrate a strong benefit from chemoradiation with significant improvements in OS and relapse-free survival (hazard ratio [HR] 1.32, 95% confidence interval [CI], 1.1-1.60; \(P < 0.0046\) and HR 1.51, 95% CI, 1.25-1.83; \(P < 0.001\), respectively). Fifty-two percent of patients who received chemoradiation relapsed, compared to 76% of patients who received surgery alone. There were similar numbers of distance relapses in both arms, which suggests that improved locoregional control with adjuvant chemoradiation might impact survivals. Moreover, no difference in long-term treatment-related toxicity was observed between the two arms.

Recently, the Korean Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial tested the role of adjuvant radiation therapy in patients with D2-resected GC.\textsuperscript{80,81} The study randomized 458 patients (stage IB–IV) to either six cycles of capecitabine and cisplatin, or two cycles of capecitabine and cisplatin, followed by chemoradiation, followed by two cycles of capecitabine and cisplatin. At a median follow-up of 7 years, there was no significant difference in disease-free survival (HR 0.74, 95% CI, 0.520-1.050; \(P = 0.0922\)) or OS (HR 1.130, 95% CI, 0.775-1.647; \(P = 0.5272\)). Locoregional failures were reduced from 13% to 7% in the chemoradiation arm. In the subgroup analysis, there was significant improvement in disease-free survival with the addition of radiation in patients with node-positive disease. Furthermore, the addition of radiation therapy to systemic chemotherapy for resectable GC was found to be of benefit over chemotherapy alone (46.7 months vs 20.9 months; \(P < 0.001\)) in a retrospective study of seven US hospitals.\textsuperscript{82} Patients with N1 disease and those with lymphovascular invasion benefited the most from radiation therapy.

While emerging evidence continues to support the use of perioperative systemic chemotherapy as the standard of care for operable GC, postoperative chemoradiation remains an alternative approach for those who
receive surgery first (with no preoperative therapy). The greatest benefit for adjuvant chemoradiation was observed in patients with node-positive disease and intestinal-type histology.

PALLIATION AND SYMPTOM MANAGEMENT

Surgeons also play an important role in scenarios of advanced GC, especially when up to 30% of patients present with locally advanced or metastatic GC. \(^{83,84}\) In these situations, patients are typically at a higher risk for malnutrition from possible tumor-related obstruction with symptoms of dysphagia or gastric outlet obstruction. In these situations, palliative procedures include gastrectomy or GI bypass, which are often reserved for the palliation of ongoing (or pending) bleeding, perforation, or obstruction.

It is important that the treating team discuss the overall goals of palliative GC surgery. While patients’ desires are prioritized, these goals should also seek to improve quality of life and allow them to continue (or not) systemic chemo-, targeted-, or immune therapy.

The impact of palliative STG versus systemic therapy alone on OS has been previously evaluated in 285 patients who were not amenable to therapeutic resections in the Dutch Gastric Cancer Trial. \(^{52}\) Of these, 129 patients did not undergo resection and had either a gastroenterostomy or an exploratory laparotomy alone, while 156 patients underwent a palliative resection. Patients in the palliative resection cohort (>70 years of age with limited metastasis to one other site) only derived a nearly 3-month survival benefit over patients who underwent a gastroenterostomy or exploratory laparotomy alone at the time of the initial DL for local or metastatic GC. This short survival benefit, however, was associated with higher morbidity (38% vs 12%) and a longer length of stay (15 days vs 10 days) in the palliative resection cohort.

In this regard, palliative GC surgery decisions should be highly personalized and driven by the patients’ goals of care, the extent of their disease progression, performance status, and multidisciplinary input from medical oncology, radiation oncology, and the palliative care teams.

GASTRIC CARCINOID
Background

Gastric carcinoids, commonly termed neuroendocrine neoplasms, are derived predominantly from mostly histamine-secreting enterochromaffin-like (ECL) cells but also serotonin-secreting ECL cells or ghrelin cells.\(^{85}\) They are classified as either a gastrin-dependent (Type I/II) or gastrin-independent (Type III) gastric carcinoids. Type I are associated with chronic atrophic gastritis (80%) whereas Type II are due to Zollinger-Ellison syndrome (ZES) (6%), often as part of the multiple endocrine neoplasia type 1 (MEN1).\(^{86}\) Type III are considered sporadic and are not associated with any syndromes nor hypergastrinemia caused by either proton pump inhibitors or by ZES. There has been an association between gastric carcinoids formation and longstanding treatment with histamine blockers which results in a hypergastrinemic state that stimulates the CCK-2 receptors on ECL cells, causing hyperplasia; in this setting, there is also a potential association of gastric carcinoids with GC.\(^{87}\) The gastrin-dependent carcinoids (Type I/II) are generally benign or low grade with a low rate of metastasis (9%-30%) whereas, sporadic gastrin-independent Type III carcinoids are more aggressive neuroendocrine carcinomas having higher rates of metastasis (54%-66%).\(^{86,88}\) Gastric carcinoids do not invade beyond the mucosa or submucosa and there are generally no signs of angioinvasion.\(^{89}\) They are graded based upon the World Health Organization 2010 classification for neuroendocrine tumors which utilizes the number of mitosis per 10 high-power fields (HPF) and the percent Ki-67 proliferation index (Fig. 31-4). Aggressive features include greater than 2 mitoses per HPF, a Ki-67 index greater than 2%, angioinvasion, and transmural invasion.\(^{87}\)
FIGURE 31-4  Ki-67 proliferation index in 50 high-power field represented by the dark brown immunohistochemistry staining.

INCIDENCE

While carcinoids can affect various organ systems, the most common site of carcinoid involvement is the GI tract (67.5%), with small intestine in 41.8%, rectum in 27.4%, and stomach in 8.7%. The age-adjusted incidence was highest in black males (4.48 per 100,000 population per year).\textsuperscript{90} Gastric carcinoids are generally diagnosed between the fifth and seventh decades with a higher overall incidence in women. The incidence of gastric carcinoid has been increasing over the past 30 years due to either improved detection with endoscopic surveillance techniques or the common use of over-the-counter proton pump inhibitors.\textsuperscript{90,91}

Presentation

Patients with gastric carcinoids often present with gastric bleeding/ulcer as presenting symptoms and are not known to be associated with carcinoid
syndrome. Type I gastric carcinoids are associated with chronic atrophic gastritis and therefore can have vitamin B12 and iron deficiency. Type I gastric carcinoids present with polyps or a mass in the fundus or body of the stomach where the gastrin-dependent ECL cells are located. Type II gastric carcinoids are associated with ZES and therefore can present with peptic ulcer disease with bleeding. Both Type I and II gastric carcinoids present generally with more than 1 tumor but these tend to be subcentimeter on initial EGD while Type IIIs are generally single tumors greater than 1 cm. Type III gastric carcinoids are generally sporadic and gastrin-independent; therefore, they are not likely to be associated with peptic ulcer disease but rather with a mass or bleeding or as an incidental finding. Gastric carcinoids are evaluated by EGD and/or EUS for level of invasion. These tumors generally stain for argyrophil, argentaffin, and chromogranin A for all types of gastric carcinoids (Fig. 31-5). Type I gastric carcinoids have a low incidence of lymphatic metastases while Type III gastric carcinoids have a high incidence (33.3% vs 71%, respectively).
FIGURE 31-5 Chromogranin A (A) and synaptophysin (B) staining using immunohistochemistry. This is a classic appearance of gastric carcinoid.

Management

The management of gastric carcinoids is optimized by a multidisciplinary approach. Gastric carcinoids are initially detected by EGD with biopsies with subsequent EUS to determine the depth of the tumor. Plasma gastrin, chromogranin A level, a 24-hour 5-hydroxyindoleacetic acid (5-HIAA) urine or fasting plasma 5-HIAA collection, and pancreastatin are obtained to complete the laboratory workup and determine the type of gastric carcinoid. Chromogranin A levels can be affected by impaired renal function, hepatic failure, chronic atrophic gastritis, or proton pump inhibitors whereas, pancreastatin is unaffected by proton pump inhibitors and is often the only elevated marker in GI carcinoids. Staging of gastric carcinoids is performed with multiphasic abdominal CT, somatostatin receptor-based imaging, and/or the recent $^{68}$Ga-labeled dotatate PET/CT. In a recent meta-analysis of the impact of $^{68}$Ga-Dotatate imaging on the management of neuroendocrine tumor, there was an overall change of 39% (range 16%-71%) even after an octreotide scan was performed.

Treatment of gastric carcinoids is based upon type of carcinoid, size, depth of invasion, presence of metastasis, and the patient’s ability to tolerate surgery. Somatostatin analogue is the medical treatment of choice for patients who are not surgical candidates due to either patient frailty or the presence of metastases. Type 1 gastric carcinoids are usually benign growths in the body or fundus of the stomach with clustering of tumors that are usually subcentimeter in size. Endoscopic mucosal resection (EMR) is the accepted treatment of choice for gastric carcinoids less than 1cm with less than five lesions without invasion beyond the submucosa. If the lesions are greater than 1cm or there are greater than five lesions, antrectomy, wedge resection, or TG are surgical options with preoperative staging CT scans performed when the lesion is greater than 2cm in size. While antrectomy may not surgically resect all the tumor, it does lower the gastrin production which can cause the tumor to regress; it is eliminated in 70% to 85% of patients. The management of Type II is similar to Type I with endoscopic, surgical, or medical treatment options but with the main focus on resecting the
gastrinoma that is the driving stimulus for these carcinoids. Type III gastric carcinoids have the worst prognosis of the three types with 5-year survival less than 50%. While EMR has been shown to be effective for tumors under 2 cm, lesions greater than this should be treated like a gastric adenocarcinoma with subtotal or TG with en bloc resection lymphadenectomy. Endoscopic surveillance is performed annually after resection or medical therapy with octreotide or lanreotide.

GASTRIC POLYPS

Background

As the use of endoscopy has increased, the incidence of gastric polyps has risen. While they are asymptomatic in more than 90% of patients, there are cases of larger polyps that cause bleeding, anemia, dyspepsia, pain, or obstruction. There are several types of gastric polyps that may appear similar grossly but differ in histology with varying neoplastic potential depending on the type and corresponding variation in appropriate initial management and follow-up.

Fundic Gland Polyp

Fundic gland polyps can be sporadic or be associated with FAP. Fundic gland polyps present as multiple transparent sessile polyps that are small (1-5 mm in diameter) and often located in the body and fundus of the stomach. Histopathology demonstrates cystically dilated glands lined by gastric body-type mucosa (Fig. 31-6). These lesions are benign with a low incidence of dysplasia (<1%) and are generally not associated with chronic atrophic gastritis or H. pylori infection. Clinical management of these polyps can include polypectomy with endoscopic surveillance, or simply surveillance alone. Sporadic fundic gland polyps do not need subsequent genetic testing for FAP as isolated polyps are not harbingers of FAP.

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Fundic gland polyps are also associated with autosomal dominant FAP in 25% to 41% as a result of the mutation of the APC gene on chromosome 5q21,\textsuperscript{104} gastric adenomatous polyps are only associated 5% of the time. Unlike the sporadic fundic gland polyps, FAP-associated polyps can be innumerable, covering the lining of the stomach; this is often referred to as familial gastric polyposis (FGP). Endoscopic surveillance including the duodenum with biopsy sampling of more than five polyps is required every 1 to 2 years until the age of 50 to determine FGP versus adenoma and to remove polyps more than 1 cm.\textsuperscript{105}

**Hyperplastic Polyps**

Hyperplastic polyps are sessile or pedunculated polyps less than 2 cm in diameter that can present as single polyp or in multiple polyps throughout the stomach (Fig. 31-7). Histologically, they are distinguished by proliferation of surface foveolar cells lining elongated, distorted pits that extend deep in to the lamina propria that contain pyloric glands, chief cells, and/or parietal cells which can overlap with the histology of hamartomas and inflammatory conditions.\textsuperscript{105} The significance of hyperplastic polyps is not their neoplastic transformation over time but rather the increased risk of synchronous GC elsewhere in the gastric mucosa. The most common clinical setting of

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**FIGURE 31-6** Hematoxylin and eosin stain of a fundic gland polyp.
hyperplastic polyps is chronic autoimmune gastritis (51.3%) and chronic infection with *H. pylori*. Less common are pernicious anemia, and reactive or chemical gastritis (37.3%). \textsuperscript{102,106} It is clinically important to biopsy locations elsewhere in the stomach at the time of biopsy of the hyperplastic polyp to rule out *H. pylori* infection or other synchronous conditions. The management of hyperplastic polyps is often debated in regards to the size cut off for polypectomy ranging from 0.5 to 2 cm given the possible faulty forceps biopsy sampling of dysplastic lesions and incidence of carcinoma in situ under 2 cm in size. \textsuperscript{107} Once a hyperplastic polyp has been noted on initial endoscopy, surveillance of the lesion is recommended at 1-year follow-up. \textsuperscript{105}

![Endoscopic image of a hyperplastic polyp](image)

**FIGURE 31-7** Endoscopic image of a hyperplastic polyp.

**Adenomatous Polyps**

Adenomatous polyps are precursor lesions to GC. While they are commonly seen in high GC countries in Asia (Korea, China, and Japan), they only account for 6% to 10% of gastric polyps in the Western population. They are
generally solitary lesions that are usually present in the antrum but not restricted to that location; they can be present anywhere in the stomach. These lesions present histologically with tubular, villous, or tubulovillous features associated intestinal metaplasia and chronic atrophic gastritis but are not due to *H. pylori*{superscript 102} (Fig. 31-8). Villous lesions that are greater than 2 cm in diameter have the highest risk of malignant transformation (28.5%-40%).{superscript 108} The management of these lesions is complete resection given that these are precursors. Repeat 6-month surveillance is recommended to detect incomplete resection and with aggressive features; 1 year is appropriate for complete resection without such features.{superscript 105}

**FIGURE 31-8** Hematoxylin and eosin staining of an adenomatous gastric polyp.

**Inflammatory Fibroid Polyps**

Inflammatory fibroid polyps are lesions that arise in the submucosa as gastric submucosal granulomas with eosinophilic infiltration. They are commonly located in the antrum or in the prepyloric region (Fig. 31-9). They present more frequently in female patients in the fifth to sixth decades of life. These lesions have the characteristics of CD34- and fascin-positive immunoreactive spindle and stellate stromal cells mixed with inflammatory cells and edema.{superscript 102} These lesions are benign but can present with bleeding, anemia, and/or obstruction, often mimicking other types of malignancies such as gastrointestinal stromal tumors (GIST).{superscript 109} Inflammatory fibroid polyps have
recently been shown to be driven by alpha-platelet derived growth factor but have a low neoplastic potential. These lesions are often amenable to endoscopic resection unless they extend into deeper layers of the gastric wall which may require wedge resection if symptomatic.

**FIGURE 31-9** Hematoxylin and eosin staining of an inflammatory gastric polyp with eosinophilic infiltration.

**Hamartomatous Polyps**

Hamartomatous polyps are rare lesions that include juvenile polyps, PJS, and Cowden disease.

**JUVENILE POLYPS**

Juvenile polyps are solitary hamartomatous polyps found in the antrum that are benign and have low neoplastic potential. They are defined histologically by irregular cysts lined by normal gastric epithelium with possible stromal hemorrhage, surface ulceration, and chronic inflammation due to torsion. However, when there are multiple polyps associated with these histological findings, they are considered juvenile polyposis. Unlike solitary juvenile
polyps, juvenile polyposis carries a malignancy risk of more than 50% due to numerous mutations (BMPR1A, 10q22.3, SMAD4, 18q21.1). Patients with SMAD4 mutation have a high probability of the combined syndrome of juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia. Routine endoscopic surveillance and polypectomy is important to reduce the risk of cancer, bleeding, anemia, and obstruction. When there is polyposis of a segment of the stomach, surgical resection may be required.

**PEUTZ-JEGHERS POLYPS**

Peutz-Jeghers polyps are the result of a rare autosomal dominant inherited condition characterized by hamartomatous GI polyps and mucocutaneous pigmentation of the lips, buccal mucosa, and digits. The incidence of Peutz-Jeghers syndrome is estimated to be from 1 in 8300 to 1 in 280,000 individuals. These polyps are histologically characterized by hyperplastic glands lined by foveolar epithelium and broad bands of smooth muscle fibers. The risk of GI cancer is significantly increased; in addition, there is a 15-fold increase in extra-GI malignancies such as breast, endometrial, pancreatic, ovarian, testicular and lung cancer. Routine endoscopic surveillance with double balloon enteroscopy (DBE) and polypectomy for polyps greater than 1 cm decreases the incidence of gastric bleeding, anemia, and/or obstruction. For extra-GI malignancies, lifelong surveillance colonoscopy, CT, magnetic resonance imaging (MRI), mammography, pelvic ultrasounds in women, and testicular examinations in men are recommended.

**COWDEN SYNDROME**

Cowden syndrome is an autosomal dominant syndrome that includes orocutaneous hamartomatous tumors; GI polyps; abnormalities of the breast, thyroid, genitourinary system; intramucosal lipomas; and ganglioneuromas. Histological findings include cystically dilated glands with papillary infoldings with a connective tissue component. The GI polyps are generally benign with low risk of malignant transformation but there is a risk of malignancy of the thyroid, colon, small bowel, genitourinary tract, breast and of non-Hodgkin lymphoma and acute myelogenous leukemia (AML).
MESENCHYMAL TUMORS

Gastrointestinal Stromal Tumors

BACKGROUND

Gastrointestinal stromal tumors are tumors that arise from the interstitial cells of Cajal and represent the most common type of mesenchymal tumors of the GI tract with the stomach being the most common site of origin. GIST has been historically misdiagnosed as GI sarcoma, leiomyoma, leiomyosarcoma, leiomyoblasomas, plexosarcoma, or malignant fibrous histiocytoma and this underestimates the true incidence in the literature in the past. Historically, the diagnosis often was associated with poor prognosis with median OS of 60 months for primary disease and 19 months for metastatic disease; however, there have been considerable advances in the diagnosis and management of GIST within the past 20 years. Since the landmark discovery of the role of proto-oncogene tyrosine kinase receptor CD117 mutations associated with GIST in 1998 by Hirota et al, the diagnosis has been significantly facilitated. Subsequent to the discovery of c-kit proto-oncogene, a new era of targeted therapy using imatinib mesylate has shaped the current management of GIST after it obtained Food and Drug Administration (FDA) approval for treatment of advanced metastatic GIST in 2002 on the basis of early clinical trials demonstrating increased progression-free survival compared to historical controls. The use of imatinib mesylate has been expanded for use in the adjuvant setting after the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial demonstrated improved recurrence-free survival for 1 year after complete resection for GIST more than 3 cm. A subsequent randomized clinical trial was performed comparing administering imatinib mesylate for 3 years versus 1 year adjuvant treatment. The trial demonstrated an improved 5-year recurrence free survival (65.6% vs 47.9%; P < 0.001) and OS (92% vs 81.7%; P = 0.02) for patients with GIST tumors having high risk features such as tumor diameter more than 10 cm, tumor diameter more than 5 cm and mitotic count more than 5/HPF, tumor rupture at time of surgery, or mitotic count more than 10 mitoses/50 HPF); on this basis, the current recommendation is to extend adjuvant therapy to 3 years.
CLINICAL PRESENTATION

Patients may present with symptoms of bleeding from submucosal ulceration of the tumor, obstructive symptoms of gastric outlet obstruction, or abdominal pain. Often asymptomatic tumors are incidentally discovered during endoscopy, radiographic imaging, or surgery for other reasons. The most common site of involvement is the stomach (60%) and small intestine (30%) with other sites along the GI tract (colon, esophagus) and extra GI tumors being less. The average size of symptomatic GIST tumors was 6 cm compared to asymptomatic tumors measuring 2 cm. Advanced GIST can present with metastatic liver lesions, invading surrounding organs, or with diffuse peritoneal involvement. Generally, GIST does not spread to the lymphatic system with exception of succinate dehydrogenase (SDH)-deficient GIST which can often have lymphovascular invasion and lymph node metastases. SDH-deficient GIST is more prevalent in pediatric GIST patients with a higher predilection for females compared to non-SDH-deficient GIST.

DIAGNOSTIC EVALUATION

Patients who present with symptoms of GI bleeding or obstruction can be initially evaluated by endoscopy with or without EUS and biopsy that can provide tissue for diagnosis of GIST and exon mutation analysis. If possible, core needle biopsy is more informative than fine needle aspiration as it provides a mitotic index profile for risk stratification. However, patients who are asymptomatic are often found incidentally on radiographic imaging for other unrelated symptoms and do not necessarily require biopsy if imaging is consistent with GIST. Contrast-enhanced CT is an appropriate staging modality to evaluate the tumor size, level of displacement of surrounding organs, heterogeneity of tumor, and metastatic disease. If there is suspicion of liver involvement, MRI of the abdomen can identify metastases. Response to targeted treatment with imatinib mesylate cause changes in resolution of enhancing tumor nodules, decreased tumor vascularity on CT, and a decrease in the [18F] fluorodeoxyglucose (FDG) PET avidity without a change in the traditional size criteria according to Response Evaluation Criteria in Solid Tumors (RECIST).
PROGNOSIS

The prognostic variables in patients with GIST have been analyzed with risk stratification systems that attempt to predict recurrence and OS. While there have been several nomograms developed by Memorial Sloan-Kettering Cancer Center (MSKCC), National Institutes of Health (NIH), and Armed Forces Institutes of Pathology (AFIP), they all reflect the variables of tumor size, mitotic count, location, and whether or not there was rupture.\textsuperscript{126–128}

Overall prognosis after initial diagnosis can be predicted using the latest nomogram by Rossi et al that factors in site of disease (stomach, small intestine, colon/rectum, other), size of tumor, and a continuous range of mitotic index to determine the 10-year OS. This had higher discriminative ability (C-index 0.72) than NIH risk stratification (C-index 0.64) or the NCCN (C-index 0.63).\textsuperscript{129}

In addition to prognostic variables of size, location, and mitotic index, genomic mutational status can provide additional prognostic information. It is important to perform a mutational analysis with exon sequencing of GIST tumors as it can predict the likelihood of response to systemic treatments. Imatinib mesylate and sunitinib are two systemic treatments available for c-kit and platelet-derived growth factor receptor alpha (PDGFRA) mutation GIST patients. Imatinib is the first-line treatment while sunitinib is second-line therapy reserved for imatinib-resistant tumors. For patients with c-kit exon-9 mutant GIST, the recommendation is to start at the higher 800 mg/d dose rather than 400 mg dose. One caveat is that wild type or PDGRFA exon 18-mutant GIST will have no response to imatinib mesylate or sunitinib.\textsuperscript{130}

GIST tumors that have exon 11 mutations will also have a higher risk of recurrence and worse overall prognosis when compared to other GIST mutations.\textsuperscript{131} However, of the patients with GIST diagnosis, 10% to 15% present as wild type GIST that lack the c-kit or PDGFRA mutation. These patients have the worst prognosis due to lack of efficacy of imatinib mesylate.\textsuperscript{132} Furthermore, 4% to 13% of all GIST patients present with BRAF mutation,\textsuperscript{133–135} a well-known oncogenic driver mutation that is also resistant to imatinib mesylate because the BRAF signaling pathway is downstream of the c-kit pathway. These patients can instead benefit from BRAF inhibitors rather than imatinib.\textsuperscript{136}
MANAGEMENT

The primary treatment for patients with resectable GIST without evidence of metastases is primary R0 surgical resection with consideration of adjuvant targeted therapy with imatinib mesylate after analysis of tumor size, mitotic rate, and location of the tumor. The indication for resection of primary GIST depends on the size with tumors more than 2 cm with EUS every 6 to 12 months if there are no concerning features (ie, large size, irregular extraluminal border, heterogeneous echo pattern, or cystic spaces) according to the National Comprehensive Cancer Network Task Force report.\textsuperscript{137} Patients who are candidates for resection should undergo careful CT inspection of the tumor for signs of metastatic disease as well as surrounding organ involvement. The surgical approach should focus on en bloc resection of the stomach and surrounding involved organs to minimize the chances of positive margins or tumor spillage. A key oncologic principle is the prevention of tumor rupture given their friable, cystic tumor structure. Patients with tumor rupture at the time of resection have a worse overall prognosis and survival when compared to those without.\textsuperscript{138} Given the low likelihood of lymph node involvement in GIST tumors, routine lymphadenectomy is not indicated; however pediatric GIST (SDH-deficient) tumors have a higher incidence of lymph node involvement and should undergo routine lymphadenectomy.

There is emerging data that minimally invasive approaches for resection of GIST are associated with lower length of stay (3 vs 8 days), fewer grade III complications (3% vs 14%), and no difference in OS versus laparotomy. There was a 10\% conversion rate in 167 minimally invasive surgery (MIS) cases compared to 230 cases that began as laparotomies (Fig. 31-10).\textsuperscript{139} At MedStar Georgetown University Hospital, preoperative planning includes gastric-tumor protocol CT to better localize the tumor and to plan port placements for a laparoscopic approach to gastric resection. We also routinely utilize a laparoscopic-assisted approach because it permits removal of gastric or small GISTs with the option to extend to a slightly longer incision, without using a longer laparotomy incision. The laparoscopic-assisted approach minimizes the risk of tumor rupture during extraction. Intraoperatively, we routinely utilize endoscopy to improve localization of the tumor during laparoscopy, confirm adequate margins during resection, and avoid narrowing the stomach when deploying a stapling device across a
lesion near the proximal or distal aspect (Fig. 31-11). While the laparoscopic approach is preferred, open surgical resection remains an accepted and safe approach. For example, patients with large GIST who are poor responders to preoperative tyrosine kinase inhibitors (TKIs), wild-type GIST, or BRAF mutated tumors usually undergo an open resection (Fig. 31-12).

**FIGURE 31-10** Laparoscopic-assisted gastrectomy with port placements demonstrate a less invasive method of gastric resection.
FIGURE 31-11 Laparoscopic wedge resection of extraluminal GIST tumor performed with intraoperative endoscopy is a minimally invasive method of resection.
Adjuvant Therapy. The role of adjuvant imatinib mesylate was defined in the landmark ACOSOG Z9001 trial, a phase III, double-blind, placebo-controlled, multicenter trial that randomized patients with more than 3 cm GIST with positive c-kit mutations to daily 400 mg imatinib mesylate daily compared to placebo. After median follow-up of 19.7 months, the imatinib mesylate group had a significant improvement in recurrence-free survival when compared to control (98% vs 83% at 1 year; \( P < 0.0001 \)). A subsequent randomized clinical trial of 3 years versus 1 year of adjuvant treatment demonstrated improved 5-year recurrence free survival (65.6% vs 47.9%; \( P < 0.001 \)) and OS (92% vs 81.7%; \( P = 0.02 \)) in patients with high risk features (tumor diameter >10 cm, tumor diameter >5 cm and mitotic count >5/HPF, tumor rupture at the time of surgery, or mitotic count >10 mitoses/50 HPF) for patients treated 3 years.\(^{120}\) The most recent trial looking at 5-year
adjuvant therapy, PERSIST-5, has now concluded. This single-arm, phase II, nonrandomized, open-label multicenter study analyzed the survival benefit of 5-year adjuvant imatinib mesylate in patients that underwent resection of primary KIT (+) GIST with high risk of recurrence within 12 weeks. The primary endpoint of the trial was recurrence-free survival. The 5- and 8-year estimated RFS rates were 90% (95% CI, 80-95) and 81% (95% CI, 62-91), respectively. The 5- and 8-year OS rate was 95% (95% CI, 86-99). Forty-five of 91 patients discontinued treatment; common reasons included patient choice (20%), adverse events (AEs, 17%), protocol deviation (4%), and loss to follow-up (4%). Of the patients that had recurrences, this occurred after discontinuing the imatinib. They concluded that patients with exon 9 or PDGFRA mutations should be started at the higher 800 mg daily dose since there was no significant benefit at 3 years at the 400 mg dose.

**Metastatic Disease.** Patients with metastatic disease are candidates for imatinib mesylate as the primary targeted therapy with the option of second-line tyrosine inhibitor, sunitinib, for disease progression after dose escalation of imatinib from 400 to 800 mg regimen. The mode of imatinib resistance has been determined to be second c-kit exon mutations in exon 13 which can be targeted by sunitinib. Patients can also develop resistance to imatinib mesylate therapy through new BRAF mutations in patients with c-kit and PDGFRA-mutant GIST. A third-line TKI, Regorafenib, is an oral multitargeted inhibitor with activity against multiple kinases including KIT, RET, RAF1, BRAF, vascular endothelial growth factor (VEGF), and PDGFR that is recommended after progression through imatinib mesylate escalation and sunitinib.

Select patients with GIST tumors that have a treatment response without signs of multifocal progressive disease (MPD) can undergo cytoreductive metastasectomy with an outcome comparable to sunitinib in highly select patients. The liver is the most common site of synchronous and metachronous metastases for patients; the incidence is 15% to 20% incidence and there is a solitary site of disease in 50% of cases. Patients selected for surgical metastasectomy are those that have stable disease who have primary or secondary resistance on first-, second-, and third-line of TKIs (imatinib mesylate, sunitinib, and regorafenib); those who have resectable disease with R0 margins; those who have good performance status (Eastern Cooperative
Oncology Group [ECOG] score 0); and those presenting with hemorrhage, perforation, obstruction, or abscess. The ability to obtain negative R0 margins enhances both progression-free survival (29 months vs 7 months; \( P = 0.002 \)) and OS (100% vs 37.5% at 1 year; \( P = 0.001 \)).\textsuperscript{148,149} While there is no consensus on the timing of metastasectomy, selection of patients who have favorable response to TKI is critical. Recent data suggests that patients who underwent resection at the period of maximum tumor response to TKIs had improved surgical outcome compared to those who were operated on after the development of primary or secondary resistance (1-year survival of 95% with stable disease, 86% with limited progression, and 0% for generalized progression; \( P < 0.0001 \)).\textsuperscript{150–152} Given the morbidity of metastasectomy, it is critical to select patients with the best probability of progression-free and OS based on the type of mutation and response to TKI.

**SARCOMA**

**Leiomyoma and Leiomyosarcoma.** Leiomyoma and leiomyosarcoma are rare mesenchymal tumors that arise from the muscularis propria and muscularis mucosa layers of the stomach and small intestine (Fig. 31-13). The diagnosis is made by immunohistochemistry. These tumors stain positive for desmin and actin but are negative for CD117 (c-kit and CD34) which distinguishes them from GIST. Leiomyosarcoma can be distinguished from leiomyoma clinically—leiomyosarcomas are typically solitary, larger, and frequently display areas of hemorrhage and necrosis. Symptoms are often delayed due to their extramural growth until there is ulceration, bleeding, obstruction, or incidental finding of metastatic disease noted in the liver and peritoneum during imaging workup for a different cause. The prognosis of patients with metastatic disease at initial presentation is poor. Management should be focused on R0 resection.\textsuperscript{153,154}
Fibrosarcoma and Angiosarcoma. Fibrosarcoma is a malignant tumor composed of fibroblasts with variable collagen production, classically with a herringbone architecture. Fibrosarcomas stain positively for vimentin and very focally for smooth muscle actin. Fibrosarcomas are rare, accounting for 1% to 3% of all sarcoma diagnoses. They present in the middle age but can also develop in infancy without any predilection for gender. Fibrosarcomas are the least differentiated type of mesenchymal malignancy and are defined as spindle cell malignant neoplasms lacking any specific differentiation and therefore are the least heterogeneous of the sarcomas. The tumors have a white or tan mass appearance with a firm texture due to the collagen content. Fibrosarcomas tend to exhibit resistance to systemic chemo- and radiotherapy.

Angiosarcomas are malignant vascular tumors that arise from normal endothelium. They comprise only approximately 2% of all sarcomas and are highly aggressive with early recurrence and metastasis. The majority develop as cutaneous tumors associated with lymphedema; less than a quarter present as deep soft tissue masses of the arm, trunk, and abdominal cavity.
Histologically, angiosarcomas have components of both epithelioid and spindled areas with a predominance of the former and are composed of sheets, small nests, cords, or rudimentary vascular channels. Immunohistochemistry positive for CD31, CD34, and von Willebrand factor confirms the diagnosis.\(^\text{157}\)

**Hemangiopericytoma.** Hemangiopericytoma is a diagnosis used to describe a wide array of neoplasms that have a thin-walled branching vascular pattern. Patients generally present with tumors of the deep soft tissue or abdominal cavity and less commonly in the limbs; symptoms are due to the mass effect from these slow growing tumors. Hypoglycemia noted in these patients when tumors secrete insulin-like growth factor.\(^\text{158}\) They are well-circumscribed masses with yellowish or tan cut surface and a fleshy or spongy consistency ranging in size from 5 to 15 cm in diameter at presentation. The overall prognosis of hemangiopericytoma is generally favorable as the majority are benign although an aggressive malignant clinical course is sometimes reported.

**Schwannoma.** Schwannoma is a benign neoplasm of Schwann cell origin. These are benign lesions that have a rubbery, yellow trabeculated appearance macroscopically. They are characterized by lymph node aggregates around their periphery, with nuclear palisading Verocay bodies and hyalinized vessels similar to schwannomas found elsewhere in the body. They grow slowly along the outer covering of the myelin sheath of the peripheral nerves and are generally contained within a capsule, permitting successful surgical removal\(^\text{159}\) (Fig. 31-14). These tumors can be monitored if asymptomatic and the diagnosis is secure.
GASTRIC LYMPHOMA

Background

There are two major types of Non-Hodgkin lymphoma—nodal involvement versus extranodal disease. Gastric lymphoma is an extranodal Non-Hodgkin lymphoma defined by the presence of the majority of the lymphoma in the stomach with variable involvement of the surrounding lymphatic drainage. The two main subtypes of gastric lymphoma are diffuse large B-cell lymphoma (DLBCL) (Fig. 31-15) or mucosa associated lymphoid tissue (MALT). Gastric lymphoma arises from the mucosa or submucosal layer, most often from the lymphoid tissue in the lamina propria.
FIGURE 31-15  Hematoxylin and eosin stain of a gastric diffuse large B cell lymphoma.

INCIDENCE

There is estimated to be 500,000 new cases of gastric lymphoma in the United States each year; this comprises 5% of all lymphoma diagnoses.\textsuperscript{160} Gastric lymphoma is the most common site of GI lymphoma followed by small intestine, ileocecum, and colon/rectum.\textsuperscript{161} Patients initially present in their sixth decade of life with more males and Caucasians than females and blacks. There are several risk factors associated with gastric lymphoma including celiac disease, \textit{H. pylori} infection, immunosuppression, human immunodeficiency virus (HIV) or Epstein-Barr virus (EBV), and inflammatory bowel disease.\textsuperscript{162,163}

PRESENTATION AND DIAGNOSIS

The clinical symptoms of patients with gastric lymphoma are nonspecific but not limited to fever, nausea, vomiting, epigastric abdominal pain, anorexia, unintentional weight loss, night sweats, hematemesis, and melena.\textsuperscript{164,165} Staging studies includes contrast-enhanced CT, MRI, EGD biopsies, EUS,
and 18F-fluorodeoxyglucose PET (18FDG-PET). Additionally, peripheral blood smear and bone marrow biopsy are required in the staging workup to exclude metastatic disease. Patients should also be tested for *H. pylori* given its essential role in the pathogenesis of MALT. There are several proposed staging systems that are available, including the Ann Arbor Staging System with Musshoff Modification and the Lugano Staging System. In the Ann Arbor Staging System with Musshoff Modification, stage IE is lymphoma restricted to the GI tract, stage IIE is lymphoma infiltrating lymph nodes on the same side of diaphragm, stage III is lymphoma involving both sides of the diaphragm, and stage IV is disseminated disease. Using the Lugano system, stage I is lymphoma confined to the GI tract, stage II is lymphoma extending into the abdomen, and stage III/IV is disseminated extranodal involvement or a GI tract lesion with supradiaphragmatic nodal involvement.

**MANAGEMENT**

The approach for patients with gastric lymphoma should be multidisciplinary, involving the medical oncologist, radiation oncologist, and surgical oncologist to determine the best treatment options. The treatment of choice for DLBCL is chemotherapy alone. A trial in Mexico randomized 589 patients to chemotherapy alone, chemotherapy plus surgery, surgery only, and surgery plus radiation therapy with 10-year survival rates of 96%, 91%, 54%, and 53%, respectively.

In contrast, there was no difference in treatment outcomes in a randomized trial of 241 patients with low-grade MALT lymphoma comparing surgery, radiation therapy, and chemotherapy with 10-year survival rates of 80%, 75%, and 87%, respectively; *P* = 0.40). Therefore, patients with low-grade MALT are offered chemotherapy with or without radiation therapy if antibiotic treatment does not cause complete regression of the MALT lesion. MALT lymphoma was first associated with *H. pylori* infection in 1991; nearly 92% of patients with MALT lymphoma are positive for *H. pylori* infections. This association is based on the T-cell activation of MALT lymphoma by *H. pylori* itself. Treatment of *H. pylori* with triple therapy (amoxicillin or metronidazole, clarithromycin, and proton pump inhibitors) has produced complete remission of MALT lymphomas and is considered the first line treatment. Surgery is reserved for those with emergency presentation of uncontrolled refractory bleeding, perforation, and/or fistula
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PERSPECTIVE ON GASTRIC CANCER

Hisashi Shinohara • Mitsuru Sasako

THEORETICAL BACKGROUND FOR D2 GASTRECTOMY

Gastric cancer remains a major health problem in East Asia. In contrast, in the United States and Western Europe, the incidence of gastric cancer has declined but is often diagnosed at an advanced stage. Thus, the number of operations that a surgeon performs annually varies according to region, so it is not easy to define which type of gastric cancer surgery should be considered the global standard. Nevertheless, a consensus that D2 dissection is the most appropriate way to treat resectable advanced gastric cancer has been reached based on the results of long-term follow-up of the Dutch D1 versus D2 trial\(^1\) and the Japan Clinical Oncology Group (JCOG) 9501 study,\(^2\) which confirmed no survival benefit with more extensive lymphadenectomy.

Radical surgery for gastrointestinal cancer focused on en bloc removal of the primary tumor along with lymphovascular drainage by excising organ-specific mesenteries. This general concept is widely accepted in colorectal cancer surgery and is realized as total mesorectal excision (TME) or complete
mesocolic excision (CME). D2 gastrectomy entails systematic dissection of all the nodes along the celiac axis (CA) and its named branches as well as the perigastric nodes. Based on embryologic principles, D2 gastrectomy is essentially a realization of mesentery-based surgery despite the anatomic restrictions inherent to the mesogastrium.

**UNIQUE ANATOMIC STRUCTURE OF THE MESOGASTRIUM**

The basic technique of lymph node dissection is common for all gastrointestinal cancers. However, because of the high incidence of tumor deposits in the adipose tissue and significant tendency of developing peritoneal metastasis in gastric cancer, dissection without destroying the intact fascial package surrounding the fatty tissue where all nodes and tumor deposits are imbedded is of paramount importance. To perform a proper lymph node dissection of the stomach, an understanding of the unique anatomic structure of the mesogastrium is essential. The stomach has 2 mesenteries: the dorsal mesogastrium and the ventral mesogastrium. During the rotation of the intestinal system, the ventral mesogastrium becomes the lesser omentum and the dorsal mesogastrium becomes the greater omentum. The mesoduodenum and the transverse mesocolon are eventually overlaid by the greater omentum. The dorsal pancreas arises from the duodenal wall, grows into the mesoduodenum, and eventually extends into the dorsal mesogastrium. The anterior surface of the mesoduodenum is then overlaid by the proper transverse mesocolon and the greater omentum. These fetal events produce certain anatomic restrictions to conduct mesentery-based gastric cancer surgery. From the viewpoint of mesenteric structures, however, it is important to recognize that regional lymph node stations can be embedded in the dorsal or ventral mesogastrium, as shown in Figure 32-1A.
FIGURE 32-1. A. Development of omentum, mesogastrium, and mesoduodenum. Numbers in circles indicate lymph node stations according to the Japanese classification of gastric carcinoma. Blue nodes belong to the ventral mesogastrium, green nodes to dorsal mesogastrium, and yellow nodes
to mesoduodenum. B. The simplified mesogastrium whose embryonic concrescences were restored. The gastric mesentery can be divided into 3 sectors: the root (R), intermediate (I), and perigastric (P) sectors. C. D2 lymphadenectomy based on mesogastric excision concept by resection of the mesogastrium while excluding the pancreas and major branches of the celiac axis (CA). ASPDA, anterior superior pancreatoduodenal artery; CHA, common hepatic artery; DP, dorsal pancreas; GDA, gastroduodenal artery; IPA, infrapyloric artery; LGA, left gastric artery; LGEA, left gastroepiploic artery; PGA, posterior gastric artery; PHA, proper hepatic artery; SGA, short gastric artery; SMA, superior mesenteric artery; SPA, splenic artery; RGA, right gastric artery; TM, transverse mesocolon; VP, ventral pancreas.

D2 DISSECTION BASED ON MESOgaSTRIC EXCISION CONCEPT

The simplified mesogastrium after restoration of embryonic concrescences is shown in Figure 32-1B. The dorsal mesogastrium can be divided into 3 sectors: the root, intermediate, and perigastric sectors. Station no. 9 surrounding the CA would be equivalent to the root sector of the whole gastric mesentery. The intermediate sector, which envelopes the pancreas, would include nodes along the left gastric artery (no. 7), common hepatic artery (no. 8), splenic hilum (no. 10), and splenic artery (no. 11). The perigastric sector would include nodes situated at the right (no. 1) and left cardia (no. 2) and lesser (no. 3a) and greater curvature (no. 4). The no. 6 infrapyloric station lies within the mesoduodenum beyond the boundary of the mesogastrium. The remaining few stations, that is, nos. 3b and 5, along the right gastric artery, and 12, along the proper hepatic artery, are originally included in the ventral mesogastrium.

The dissection of N2 nodes by “complete” mesogastric excision with central vascular ligation like CME is disturbed by the presence of the pancreas and some branches arising from the CA. Ligation of the CA in radical gastrectomy is anatomically possible since the blood supply to the liver is secured in most cases by the pancreatoduodenal arcades from the superior mesenteric artery. However, by preserving the gastroduodenal artery, even Appleby’s operation cannot realize complete mesogastric excision. Further, the division of the CA entails combined
splenopancreatectomy even when the organs are not directly invaded. Instead, as shown in Figure 32-1C, D2 gastric cancer surgery should aim at systematic mesogastric excision, that is, en bloc excision of the mesogastrium while excluding the pancreas and its associated vessels. This concept is expected to aid the universalization of the operative strategy for gastric cancer, as is currently the case for TME and CME in colorectal cancer.

**PRACTICAL MODIFICATIONS OF D2 GASTRECTOMY**

Prognostic relevance of other components of the standard D2 dissection such as combined splenectomy in case of cancer of the upper third stomach (JCOG 0110) and bursectomy (JCOG 1001) has more recently been addressed by randomized phase III trials. In the past, when most of gastric cancers were large and accompanied by large nodal metastasis surrounding the left gastric, splenic, and celiac arteries, en bloc resection of the entire tumor required the combined resection of the pancreatic tail with the spleen. This procedure, which had been carried out for prophylactic dissection of the splenic artery and hilar lymph nodes, was abandoned because of the higher mortality and morbidity with limited survival benefit compared with pancreas-preserving total gastrectomy. Now, such extended surgery is used only for T4b tumors invading the pancreas or splenic vessels. JCOG 0110, a randomized controlled trial comparing a total gastrectomy with or without splenectomy for advanced gastric cancers not involving the greater curvature, proved the noninferiority of spleen preservation for such tumors, while 2 other small sized trials did not show any statistically reliable results. To carry out a D2 dissection without splenectomy, meticulous dissection along the splenic vessels is needed. For safe dissection of this area, accurate knowledge of the basic anatomy and its variations is essential. The branch-off point of the posterior gastric artery varies widely; it is sometimes at 3 to 4 cm from the root of the splenic artery and sometimes close to the splenic hilum. We should know that the upper pole artery to the spleen sometimes has a common trunk with the posterior gastric artery, which should be divided not at the root of the common trunk but at the branching off from the upper pole artery. There are 3 or 4 short gastric arteries, each of which tracks ventrally from the final branches of the splenic artery into the splenic parenchyma. The
left gastroepiploic artery is usually the most caudal branch of the splenic artery. Often, it has a common trunk with the inferior pole branch to the spleen. As demonstrated in Figure 32-2A, all nodes are included in the dorsal mesogastrium that expanded into the upper abdomen to form the omental bursa. The role of bursectomy dissecting the peritoneal lining covering the pancreas and the anterior layer of the transverse mesocolon for preventing peritoneal metastasis had long been controversial. However, a phase III trial (JCOG 1001) failed to demonstrate a significant role of bursectomy in survival of patients with T3/T4 gastric cancer. \textsuperscript{11}
FIGURE 32-2. A. Sagittal transaction near the root of the splenic artery and 3-dimensional scheme of the structures left lateral to the transection. All lymph nodes along the splenic vessels and posterior gastric vessels and in the splenic hilum are included in the dorsal mesogastrium that was expanded into the upper abdomen to form the omental bursa. Numbers in circles indicate lymph node stations according to the Japanese classification. Ao, aorta; LGEA, left gastroepiploic artery; LRV, left renal vein; PEA, posterior epiploic artery; PGA, posterior gastric artery; SPA, splenic artery. B. Sagittal transactional scheme near the origin of the right gastroepiploic vessels. Anatomic structures of the greater omentum, transverse colon and mesocolon, pancreas head, and duodenum are shown with vessels surrounding the organs. The ventral mesoduodenum includes the supraduodenal vessels, and the dorsal mesoduodenum includes infrapyloric vessels. The origins of the dorsal mesoduodenum and mesogastrium share the common root that joins with the right gastroepiploic vein (RGEV), the anterosuperior pancreatoduodenal vein (ASPDV), and the accessory right colic vein (ARCV), making Henle’s common trunk. GDA, gastroduodenal artery; IPA, infrapyloric artery; PV, portal vein; RGEA, right gastroepiploic artery; SDA, supraduodenal artery; SMV, superior mesenteric vein.

The last part of the antrum (4-6 cm) and the first portion the duodenum (duodenal bulb) are dually supplied by the infrapyloric vessels in the dorsal mesoduodenum\(^\text{12}\) and by the supraduodenal vessels in the ventral mesoduodenum (Fig. 32-2B). To treat an antral cancer, proper dissection of both the mesogastrium and the mesoduodenum is essential. The incidence of metastasis to the infrapyloric node station is nearly 50% for distal cancers of T2 or more, and more than 40% of those having such metastasis will survive more than 5 years after proper D2 dissection.\(^\text{13}\)

THE PLACE OF LAPAROSCOPIC AND ROBOTIC SURGERY

Reflecting the result from the JCOG 0703 phase II study that explored the feasibility of the laparoscopic distal gastrectomy for stage I gastric cancer, the Japanese Guidelines for the Treatment of Gastric Cancer revised the position of laparoscopic distal gastrectomy for stage I gastric cancer in 2014 from a promising but experimental treatment to a valid option in daily clinical practice.\(^\text{14}\) Thereafter, surgeons in East Asia have proceeded to conduct large
randomized controlled trials comparing open versus laparoscopic surgery and have gradually extended the indication to more advanced cancers.\textsuperscript{15,16} In many respects, however, laparoscopic surgery has limitations, including lack of tactile sensation; difficulty in widely spreading out the membranes, which is essential for proper D2 dissection; and longer learning curve. Considering the high tendency to develop peritoneal metastasis and extranodal metastasis in the adipose tissue,\textsuperscript{6} application of laparoscopic surgery for T3/4 tumors should be carefully considered until noninferiority of this approach to open surgery is proven. The recent development of surgical robotics represented by the da Vinci System may have overcome several shortcomings inherent to the laparoscopic approach. This system has advantages compared with conventional laparoscopic surgery systems, such as the EndoWrist, including additional degrees of freedom, elimination of the fulcrum effect, and high-resolution 3-dimensional images that can be magnified and reduce human tremor. Decrease in the incidence of surgical complications when compared with laparoscopic surgery has been reported from a leading Japanese institution.\textsuperscript{17} However, a nonrandomized prospective study that compared robotic surgery with laparoscopic surgery in Korea has shown morbidity to be extremely low in both approaches, but the robotic surgery required a longer operating time and was significantly more expensive.\textsuperscript{18} Another retrospective comparison of robot-assisted and laparoscopy-assisted pylorus-preserving gastrectomy also demonstrated no benefit of robotic over laparoscopic surgery.\textsuperscript{19} Given the shorter learning curve for acquisition of relevant surgical skills,\textsuperscript{20} easier access to robotic surgery and more frequent opportunities for training will be indispensable for the future progress of this promising modality.

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GASTROINTESTINAL STROMAL TUMORS
Nicole J. Look Hong • Chandrajit P. Raut

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare neoplasms. Although they represent only 0.1% to 3% of all gastrointestinal malignancies,1–4 they account for 80% of gastrointestinal mesenchymal neoplasms.5 Approximately 5000 to 6000 new cases are diagnosed per year in the United States, for an annual incidence of 14.5 per million and prevalence of 129 per million.6 In the last 15 years, the understanding and treatment of GIST has witnessed remarkable advances due to two key developments: (1) the identification of constitutively active signals (oncogenic mutation of the c-KIT and platelet-derived growth factor alpha [PDGFRA] gene-encoding receptor tyrosine kinases) and (2) the development of therapeutic agents that suppress tumor growth by specifically targeting and inhibiting these signals. These developments in the management of GIST illustrate the principle of translational therapeutics in oncology, confirming that specific inhibition of tumor-associated receptor tyrosine kinase activity is an effective cancer treatment. The advent of effective targeted medical therapy for GIST has
increased the complexity of management and opened new dialogues regarding the need for integrated multimodality therapy. This chapter reviews the biology, treatment, and emerging clinical challenges of these mesenchymal neoplasms.

**PATHOLOGIC FEATURES**

**Historical Background**

The term “GIST” was initially coined in 1983 by Mazur and Clark to describe intra-abdominal nonepithelial neoplasms which lacked the ultrastructural features of smooth muscle cells and the immunohistochemical characteristics of Schwann cells. \(^7\) GISTs typically exhibit heterogeneous histologic features. They are most commonly composed of long fascicles of spindle cells with pale to eosinophilic cytoplasm and rare nuclear pleomorphism, but may occasionally exhibit epithelioid characteristics, including sheets of round- to oval-shaped cells with abundant eosinophilic cytoplasm and nuclear atypia (Fig. 33-1). As such, they are typically classified as spindle cell type, epithelioid type, or mixed type. The majority of GISTs are of spindle cell appearance (70%), while epithelioid (20%) and mixed (10%) cell morphology are less common.

**FIGURE 33-1** GIST histology. Staining of tumor paraffin sections with hematoxylin and eosin (H&E) reveals three patterns of GIST histology: (A) spindle cell, (B) mixed cell, and (C) epithelioid cell type.

In 1995, Miettinen and colleagues discovered that 70% of GISTs were positive for CD34 by immunohistochemistry, a myeloid progenitor cell
antigen also present in endothelial cells and fibroblasts. Based upon their histologic features, GISTs are believed to arise from the interstitial cells of Cajal, components of the intestinal autonomic nervous system that serve as intestinal pacemakers and also express CD34. Nonetheless, until the late 1990s, there were no objective criteria to classify GISTs. They were frequently misclassified as leiomyomas, leiomyoblastomas, leiomyosarcomas, Schwannomas, gastrointestinal autonomic nerve tumors, or other similar soft tissue histologies. Consequently, interpretation of clinical results for reports on “GISTs” published before 2000 is challenging.

**Receptor Tyrosine Kinase Mutations**

In a landmark publication in 1998, Hirota and colleagues reported two critical findings: (1) near-universal expression of the transmembrane receptor tyrosine kinase KIT in GISTs and (2) presence of gain-of-function mutations in the corresponding c-KIT proto-oncogene. The KIT receptor is activated by binding its cytokine ligand, known as steel factor or stem cell factor, which then causes receptor homodimerization, phosphorylation, and cellular proliferation. KIT plays a critical role in the development and maintenance of components of hematopoiesis, gametogenesis, and intestinal pacemaker cells. Oncogenic KIT mutations have been identified as molecular drivers of neoplasms corresponding to these functions, including mast cell tumors, myelofibrosis, chronic myelogenous leukemia, germ cell tumors, and GIST. Mutated KIT remains constitutively active even in the absence of ligand binding and results in both unregulated cell growth and malignant transformation.

GISTs are identified by immunohistochemical staining for the CD117 antigen, part of the KIT receptor (Fig. 33-2). CD117 expression is characteristic of most GISTs, but not of other gastrointestinal smooth muscle tumors such as leiomyosarcoma, which are more likely to express high levels of desmin and smooth muscle actin. Application of CD117 staining as a diagnostic criterion for GIST has heightened understanding of disease prevalence but is an imperfect isolated surrogate for GIST diagnosis. Some GISTs may stain strongly for KIT (CD117) by immunohistochemistry (KIT-positive) yet lack KIT mutations, while others that do not stain for KIT (KIT-negative) may nevertheless harbor KIT mutations.
Immunohistochemistry to detect expression of KIT (CD117) is present in approximately 95% of GIST and varies among tumors from predominantly cytoplasmic (left), to perinuclear and dot-like (right). Variable expression within a given tumor also occurs (right).

Over 85% of GISTs have activating KIT mutations (Fig. 33-3). These mutations commonly occur in exon 11 (in 57% to 71% of cases), exon 9 (10% to 18%), exon 13 (1% to 4%), and exon 17 (1% to 4%). GISTs with KIT exon 9 mutations predominantly arise in the small intestine, and homozygous mutant GISTs are often associated with recurrent disease. Mutations in exon 11 may include deletions, insertions, single-base substitutions, and various combinations of these and are associated with variable rates of disease recurrence following complete resection. Deletion mutations in exon 11 are an independent adverse prognostic factor, with worse prognosis than those with point mutations. Deletions specifically involving codon 557 and 558 are considered mutational “hotspots” and are associated with more aggressive and often metastatic behavior.
KIT and PDGFRA mutations in GIST. KIT and PDGFRA mutations in GIST produce constitutive ligand-independent receptor activation. Response to tyrosine kinase inhibitors correlates with the location of the activating mutation, with best response in patients whose tumors contain mutations in KIT exon 11.

Approximately 35% of neoplasms lacking KIT mutations have activating mutations in a gene encoding a related receptor tyrosine kinase, the platelet-derived growth factor receptor alpha (PDGFRA).\(^{31-33}\) PDGFRA mutations have been identified in exon 12 (1% to 2% of GISTs), exon 18 (2% to 6%), and exon 14 (<1%).\(^{31,34}\) KIT and PDGFRA mutations are mutually exclusive events in GIST pathogenesis. However, no differences in the activation of downstream signaling intermediates have been observed between PDGFRA-mutant and KIT-mutant tumors, suggesting that both pathways result in parallel oncogenic molecular signals. Substitution of valine (V) for aspartic acid (D) at codon 842 in exon 18 accounts for 70% of all PDGFRA mutations and is associated with imatinib resistance.\(^{35}\) GISTs harboring a PDGFRA exon 18 D842V mutation have been shown to have a gastric location predilection, have a lower risk of recurrence than GISTs with KIT mutations, and tend to have a more indolent course.\(^{36}\)

Finally, wild-type (WT) GISTs exhibit no detectable KIT or PDGFRA mutations, and have alternate pathways for pathogenesis. Additional putative mutations have been identified to molecularly characterize this group of emerging GIST tumors. These include mutations in BRAF V600E exon 15 and insulin-like growth factor-1 receptor overexpression.\(^{37,38}\) Mutations in
succinate dehydrogenase (SDH) subunits and type 1 neurofibromatosis (NF1) genes have also been linked with GIST oncogenesis (see discussion below).  

**EPIDEMIOLOGY**

**Incidence**

Investigators have attempted to determine the true incidence of GIST using the Surveillance, Epidemiology, and End Results (SEER) database from the National Cancer Institute. However, these data are difficult to interpret since many GISTs were previously misclassified as other gastrointestinal mesenchymal neoplasms. Although a near doubling of the incidence of all gastrointestinal mesenchymal tumors (over 80% were GIST) has been reported (0.17/100,000 in 1992 to 0.31/100,000 in 2002), this may be due to a combination of increased recognition, increased screening, and/or true increased incidence. The annual incidence in the United States is estimated to be approximately 5000 new cases per year. European population-based studies identify annual incidence rates ranging from 11 to 14.5 cases per million population.

**Age**

The median age at diagnosis of GIST is 60 years (range 58-65 years). There is a slight male predominance, and there is no significant racial or ethnic predilection. GIST does occur rarely in children (1.4%-2.6% of cases), often as a familial syndrome or as part of Carney’s triad (see below). The clinical presentation is typically different in children and tends to present with multifocal epithelioid gastric GISTs, harbor wild-type KIT/PDGFRA genes, and have a higher incidence of lymph node metastases.

**Hereditary GIST**

The overwhelming majority of GISTs are sporadic. Nevertheless, families with germline KIT and PDGFRA mutations have been reported. Individuals with GISTs secondary to familial germline KIT mutations are
usually younger than those with sporadic GISTs, manifest multifocal disease at presentation, and rarely develop metastatic disease. This phenotype includes skin hyperpigmentation and diffuse hyperplasia of the intestinal myenteric plexus and is associated with a germline KIT exon 11 mutation. Mutations in exons 8, 13, and 17 have also been identified at the germline level with constitutive activation resulting in variable phenotypes including dysphagia, urticarial pigmentosa, and macrocytosis.

Germline PDGFRA mutations are less common and have been reported to affect exon 12. These individuals have congenitally enlarged hands, small intestinal polyps, fibroid tumors, and lipomas.

Von Recklinghausen neurofibromatosis type 1 (NF1) is the most common autosomal dominant inherited disorder and is characterized by a spectrum of clinical features including cutaneous neurofibromatosis, café-au-lait macules, axillary and inguinal freckling, ocular hamartomas, and benign and malignant intestinal tumors. Approximately 7% of these individuals have multifocal GISTs, most commonly in the small intestine. In addition to their NF1 mutations, these individuals express KIT and PDGFRA point mutations in 8% and 6% of GISTs, respectively. Conversely, NF1 mutations have not been identified in non-NF1 individuals with sporadic GISTs.

Gastric GISTs are components of both Carney’s triad and Carney–Stratakis syndrome. Fewer than 100 cases of Carney’s triad, consisting of gastric GISTs, pulmonary chondromas, and extra-adrenal paragangliomas, have been reported. Esophageal leiomyomas and adrenal cortical adenomas have recently also been added as elements of this syndrome. Approximately 85% of cases occur in women and 80% are diagnosed before age of 30. Patients with Carney’s triad lack germline KIT or PDGFRA mutations; however, chromosome 1 deletions of 1q12 to 1q21 involving the SDH gene and the 1p region have been implicated in the pathogenesis of this syndrome. GISTs seen in these patients are typically multifocal and are more likely to manifest lymph node metastases.

The similarly eponymous Carney–Stratakis syndrome describes familial cases expressing the dyad of gastric GIST and paraganglioma. Recently, inactivating germline mutations in several SDH subunits have been reported in Carney–Stratakis syndrome kindreds and are reflected as a characteristic clinical picture.
CLINICAL PRESENTATION

Primary GISTs commonly arise in the stomach (50% to 70%), small intestine (25% to 35%), colon and rectum (5% to 10%), mesentery or omentum (7%), and esophagus (<5%). Occasionally, GISTs may arise in the duodenal ampulla, appendix, gallbladder, and urinary bladder.

GISTs are generally found due to symptoms. In a large population-based study, 69% of tumors were symptomatic, 21% were discovered incidentally at surgery, and 10% were discovered at autopsy. Primary extragastrointestinal GISTs are rare (<10% of cases) and may be the sequela of a yet unrecognized primary gastrointestinal tumor. These GISTs usually present in the omentum or mesentery and have a more aggressive clinical course compared with similar-sized gastric counterparts.

GISTs are often highly vascular, soft, and friable, and bleeding is therefore a common complaint. Other common presenting symptoms may include abdominal pain, distension suggestive of obstruction, or a palpable mass. GISTs may cause life-threatening hemorrhage by erosion into the gastric or bowel lumen. Alternatively, tumor rupture may cause potentially catastrophic intraperitoneal bleeding and/or dissemination by peritoneal seeding. Intestinal obstruction may lead to perforation. Small tumors may remain asymptomatic and be incidentally detected on radiographic studies, endoscopy, or laparotomy.

Between 15% and 47% of patients with GIST have metastatic disease at diagnosis. Common sites of metastasis include liver, peritoneum, and omentum; lymph node metastases are rare. Extra-abdominal metastases (lung, bone, subcutaneous tissues, and brain) are rare, observed in approximately 5% of patients.

DIAGNOSIS

Radiographic Studies

The initial imaging study for a suspected or confirmed GIST is a contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis. Primary GISTs are typically well-circumscribed masses located within the
wall of hollow viscera and may appear heterogeneous due to the presence of necrosis or intratumoral hemorrhage, particularly in large tumors (Fig. 33-4). Magnetic resonance imaging (MRI) may help to characterize metastases to the liver or primary perirectal disease (Fig. 33-5). $^{[18]}$F-fluoro-2-deoxy-D-glucose positron emission tomography combined with CT (FDG PET-CT) may be helpful to characterize masses that are ambiguous on CT, to monitor response to tyrosine kinase inhibitor therapy, and to detect emergence of drug-resistant clones. However, its diagnostic test characteristics are sensitive but not specific, a profile that is not recommended for initial identification or staging of suspected primary disease. $^{74–76}$

FIGURE 33-4 CT image of primary gastric GIST presenting as an exophytic mass (arrow) off of the greater curvature of the stomach.
Endoscopy, Fine-Needle Aspiration, and Biopsy

Endoscopically, a primary GIST may appear as a submucosal lesion, with or without ulceration, present in the upper or lower gastrointestinal tract. They are often indistinguishable from other gastrointestinal tumors of smooth muscle origin, such as leiomyomas (Fig. 33-6). Endoscopic ultrasound (EUS) is not necessary to evaluate a confirmed GIST. However, EUS-guided fine-needle aspiration (FNA) may be attempted to establish diagnosis. Nevertheless, EUS-FNA is not consistently diagnostic, with sensitivity approaching 80%. Additional cytologic morphology, immunohistochemistry, and reverse-transcriptase polymerase chain reaction analysis for KIT mutations may be required to confirm a diagnosis.
A preoperative biopsy is not routinely necessary for a primary, resectable neoplasm suspicious for GIST, particularly in the setting of ongoing symptoms. In fact, preoperative biopsy, either endoscopic or percutaneous, may rupture a suspected GIST and increase risk of dissemination and bleeding. However, if the differential diagnosis includes entities such as nonoperatively treated lymphoma, if preoperative diagnosis is required for targeted neoadjuvant therapy, or if there is suspected metastatic disease, biopsy is warranted.

STAGING

The American Joint Committee on Cancer (AJCC) implemented formal staging for GISTs in 2010. This schema is divided into two main groups based on location: gastric GISTs (also used for omentum), and small intestine GISTs (also used for esophagus, colorectal, mesentery, and peritoneum). This dichotomy is based on evidence of prognostic differences based on anatomic location. The tumor, node, metastasis (TNM) classification is combined
with mitotic rate to determine individual tumor stage. Germline mutational status is not included in the current AJCC classification. This staging system has been validated and correlates with disease-free survival and overall survival, with tumor size and mitotic index being the most important prognostic factors.⁸³

**PROGNOSTIC FACTORS AND RISK STRATIFICATION**

The three established pathologic prognostic factors related to the risk for GIST metastases are tumor size, mitotic index (per 50 high-power field [HPF]), and tumor site of origin, with mitotic count being the most contributory (Table 33-1).¹⁶,⁸⁰,⁸⁴ While tumors under 1 cm appear to be at a low risk of recurrence and progression, no tumors can be definitively called benign and most have malignant potential. Individuals with small bowel or colorectal GISTs have a higher risk of progression than those with gastric GISTs of comparable size and mitotic count. Several risk stratification schema have been suggested to categorize patient prognosis and recurrence risk based on pathologic features (Table 33-2).⁸²,⁸⁵–⁸⁷ However, predicting tumor behavior based on pathologic elements alone is suboptimal, and contemporary risk stratification aims to combine these features with molecular analysis in order to glean a more complete picture of biologic potential.

**TABLE 33-1: RISK ASSESSMENT FOR PRIMARY GASTROINTESTINAL STROMAL TUMORS**⁸⁴
Additional adverse prognostic factors suggested include high cellular proliferation index (Ki-67), aneuploidy, telomerase expression, KIT exon 9 mutations, and KIT exon 11 deletions involving amino acid W557 and/or K558. Point mutations and duplications of KIT exon 11 appear to have a favorable prognosis. Exon 9 and 11 mutational status have also been shown to predict response to medical therapy and thereby influence clinical rates of progression and survival. In advanced GIST with KIT exon 11 mutations, approximately 90% of patients will respond to imatinib, whereas only 50% of exon 9 mutations will have a similar response, although dose-related response rates may be observed in the latter. Most GISTs with
**PDGFRA** mutations have a lower risk of recurrence and respond to imatinib, with the exception of the D842V substitution in exon 18.\(^{35}\) Despite these mutational correlations with recurrence risk, evidence suggests that standard pathologic prognostic factors, particularly mitotic count, predict clinical outcomes more accurately than mutational analysis status, suggesting that no individual factor should be used in isolation.\(^{25}\)

Completeness of surgical resection has also been suggested as a prognostic indicator. However, the ideal margin of resection is unknown. While a macroscopically complete resection with negative or positive microscopic margins (R0 or R1 resection, respectively) is associated with a better prognosis than a macroscopically incomplete resection (R2 resection), there are no data to confirm that a positive microscopic margin (R1 resection) impacts survival.\(^{2}\)

**THERAPY FOR PRIMARY DISEASE**

The modern management of GISTs is a multidisciplinary task. Patients should be treated in a center offering expertise in the surgical and medical management of disease, with available multidisciplinary cancer conferences to discuss nuances in clinicopathologic and immunohistochemical tumor profile and its influence on multimodality treatment sequencing.

**Active Surveillance**

The management of gastric GISTs less that 2 cm in diameter is controversial, as their natural history is not known with certainty but is thought to be favorable. Two studies have shown that sub-centimeter gastric GISTs (microGISTs) are relatively common, detected in 22.5% of autopsies in adults over the age of 50 in Germany, and in 35% of patients undergoing gastrectomy for gastric cancer in Japan.\(^{93,94}\) Despite their relative frequency, few of these neoplasms appear to become clinically relevant. Until further data are available, the most appropriate management of such small tumors remains uncertain.

In an Italian study comparing 170 GISTs ≤2 cm in size to 101 >2 cm, the frequency of mitoses observed in individual tumors increased from 20% in <6 mm GISTs to 75% in 1.7- to 2.0-cm GISTs to 100% in >2-cm GISTs.\(^{95}\)
Of the 170 small GISTs, 135 underwent mutational analysis. Key findings compared to larger GISTs were that 74% of small GISTs had *KIT* or *PDGFRA* mutations with an excess of wild-type cases, *KIT* exon 11 mutations were less common, and novel mutations were observed that have not been reported in clinically relevant GISTs >2 cm.95

Gastric tumors stratified as low risk based on clinical, pathologic, and molecular features may be considered for active surveillance alone. Decisions for surveillance alone should involve a multidisciplinary discussion with risks and benefits provided to the patient and documented in the medical record. Clinical and radiologic parameters invoking a transition to more aggressive management should also be reviewed.

If active surveillance is undertaken, current National Comprehensive Cancer Network (NCCN) guidelines suggest endoscopy with esophagogastroduodenoscopy (EGD) +/- EUS every 6 to 12 months. Presence of lesional growth to >2 cm, irregular extraluminal borders, ulceration, heterogenous echogenic foci, presence of cystic spaces, and/or development of symptoms should prompt reconsideration of the management strategy.96 European Society for Medical Oncology (ESMO) guidelines recommend annual surveillance with EUS for presumed <2 cm GISTs, and EUS-FNA may be offered.97 If a diagnosis of GIST is confirmed, then surgery should be offered. If the patient prefers no surgery, then observation should continue, though an evidence-based optimal surveillance policy is lacking.97

Japanese guidelines have been developed based on extensive population-based endoscopic surveillance for gastric cancer and distinguish between EGD and EUS findings. Gastric submucosal tumors <2 cm without the malignant findings on EGD of ulceration, irregular margins, or rapid growth may be followed with EGD surveillance once or twice per year.98,99 Tumor growth or presence of malignant findings on EGD warrants either surgery or further workup, including CT, EUS, or EUS-FNA. Malignant findings on EUS (heterogeneous parenchyma or irregular margins) or confirmation of GIST by EUS-FNA are indications for surgery. Patients with submucosal lesions without confirmation of a diagnosis of GIST and without malignant findings on EUS may be offered surgery or ongoing surveillance.

**Surgery**
Surgery remains the standard of care and the only potentially curative option for patients with primary, resectable, localized GISTs. All patients with GISTs ≥2 cm, symptomatic tumors, and all GISTs of non-gastric origin should be considered for surgical resection and adjuvant medical treatment. Oncologic principles of safe surgical practice prevail, and the primary goal of the operation is to resect all tumor with macroscopically and microscopically negative margins (R0). Tumors should be handled with a “no-touch” technique, as rupture or violation of the tumor pseudocapsule during surgery is associated with increased risk of recurrence and bleeding. Formal lymphadenectomy is rarely required, except in pediatric populations where lymph node metastases may be more prevalent.\(^{100,101}\)

The extent of surgical resection is governed by the size of the tumor in relation to anatomic location, and the ability to safely restore gastrointestinal continuity. Sphincter and organ preservation is preferred, although locally advanced GISTs should be approached with an en bloc resection of adjacent organs in order to minimize potential violation of the tumor, if necessary. In such cases, surgical resection is often preceded by medical therapy to promote tumor shrinkage and minimize the extent of resection, as described below. The extent of surgery is usually a wedge or segmental resection of the involved stomach or bowel, without the wide margins necessary for corresponding adenocarcinoma. In a series of 140 patients with gastric GISTs, wedge resections were performed in 68%, partial gastrectomies in 28%, and total gastrectomies in only 4%.\(^{102}\) Occasionally, more extensive resection (total gastrectomy for a large proximal gastric GIST, pancreaticoduodenectomy for a periampullary GIST, or abdominoperineal resection for a low rectal GIST) may be necessary.

Regardless of whether an open or laparoscopic resection is planned, GISTs are approached in a similar fashion using preoperative imaging as a guide. The abdomen is first thoroughly explored to identify involved organs and remove any previously undetected peritoneal metastatic deposits. Although primary GISTs may demonstrate inflammatory adhesions to surrounding structures, they do not generally invade other organs beyond the site of origin, despite ominous CT appearance. Nasogastric suction, preoperative tattooing, and intraoperative EGD can be considered as adjuncts to assist in the accurate localization of the GIST and in the achievement of R0 resection.

Although endoscopic resection of small gastric GISTs has been reported,
this is not recommended. Unlike early gastric adenocarcinomas limited to the mucosa and amenable to endoscopic mucosal resection, GISTs involve the muscularis propria. Therefore, endoscopic resection risks leaving a positive deep margin, and due to the depth of the lesion may result in gastrointestinal perforation. Such endoscopic resections have been reported for the most part for small GISTs, a group of tumors for which surgery may not even be indicated. Therefore, such techniques should be approached with a great deal of caution and are not recommended by any major international guidelines.

Laparoscopic or laparoscopy-assisted resection of primary GISTs continues to evolve and may be considered if standard oncologic principles can be maintained (Fig. 33-7). Two early studies confirmed both the safety and feasibility of a laparoscopic approach. A recent meta-analysis by Koh et al. supports laparoscopic resection as a safe and feasible approach with no differences in margin positivity, recurrence-free survival (RFS) or overall survival (OS) when compared to open resections. Additionally, laparoscopic resections frequently had shortened stays in hospital and lower intraoperative blood loss. However, decisions for technical operative approach must balance perioperative factors with oncologic safety. Evaluation of patient comorbidity, anatomic tumor location, surgeon expertise, and ability to convert to an open approach should be included in preoperative decision-making. When laparoscopic and laparoscopy-assisted approaches are undertaken, modified lithotomy or split-leg positioning should be considered for heightened visualization and organ manipulation. In addition, an angled camera and roticulating laparoscopic stapler may assist in the safe resection and extraction of the tumor.
FIGURE 33-7 Laparoscopic image of gastric GIST along greater curvature of stomach (arrows) isolated between traction sutures (A) and with stomach
partially divided using linear stapler (B).

The goal of surgery for GIST is to perform a margin-negative resection. However, unlike for visceral adenocarcinomas or sarcomas at other sites, wide margins are unnecessary. Wide margins beyond a R0 resection have not been definitively linked with improvements in survival or recurrence, particularly in the era of effective medical therapy. There are also no data indicating that patients with an R1 (microscopically involved) resection require re-excision.\textsuperscript{41} Margins may retract after resection and chemical fixation, and the pathologist may resect a staple line ex vivo, thereby converting a microscopically negative margin into a positive one. As such, all cases of positive microscopic margins should be reviewed by a multidisciplinary team to assess the need for re-excision with careful consideration of anatomic feasibility, biologic risk profile, and patient comorbidity.

**OUTCOMES**

Despite macroscopically complete resection, as many as 50\% of individuals may develop recurrent disease at a median of 24 months.\textsuperscript{2,108} An R0 or R1 resection is associated with 5-year OS rates of 34\% to 63\%, whereas R2 resection is associated with 5-year OS as low as 8\%.\textsuperscript{1,2,109,110} However, these series do not apply current standards of adjuvant medical therapy and are likely underestimates of contemporary survival rates.

**Neoadjuvant Therapy for Primary Disease**

The development of the effective, well-tolerated, orally available targeted tyrosine kinase inhibitor (TKI), imatinib mesylate (STI571, Gleevec, Novartis Pharmaceuticals) has revolutionized the treatment of GIST. This agent was initially developed for the management of patients with metastatic disease; however, suggested efficacy in neoadjuvant and adjuvant settings has greatly expanded its clinical utility. Imatinib selectively inhibits several tyrosine kinases, including KIT, PDGFRA, and BCR-ABL.\textsuperscript{20,111,112} Several clinical trials have confirmed that up to 80\% of patients with metastatic GIST achieve a complete or partial response or demonstrated stable disease on imatinib.\textsuperscript{113,114} This prompted initial consideration of imatinib use as a tool to
promote tumor shrinkage and facilitate surgical resection.

There are several scenarios to support the neoadjuvant use of TKI in GISTs. While neoadjuvant therapy may not change the extent of gastric resection required, it may convert an operation requiring an open laparotomy to one performed laparoscopically or laparoscopy-assisted. In addition, in cases with locally advanced and/or unresectable tumors, imatinib is the first-line therapy, with intent to reconsider the role of surgical therapy after at least 6 months. After tumor shrinkage, individuals may be amenable to R0 resection, sphincter preservation, and/or organ sparing.

The role of neoadjuvant therapy with imatinib followed by surgical resection has been explored in several trials. In 2009, the Radiation Therapy Oncology Group (RTOG) 0132 phase II trial was the first multi-institutional, prospective study evaluating the use of neoadjuvant and adjuvant imatinib in the treatment of primary GIST (tumors ≥5 cm; group A) and recurrent or metastatic GIST (tumors ≥2 cm; group B). Patients were treated with imatinib (600 mg/day) for 8 to 12 weeks prior to surgery and then maintained on adjuvant imatinib for 2 years (Table 33-3). Preoperative imatinib therapy resulted in stable disease in 83% and 91% of patients in group A \((n = 30)\) and group B \((n = 22)\), respectively. Long-term follow-up results have shown an estimated 5-year progression-free survival (PFS) and OS of 57% in group A, 30% in group B, and 77% in group A, 68% in group B, respectively. Two- and 5-year disease-specific survival (DSS) rate estimates for group A were 93.5% and 76.9% and for group B were 90.9% and 68.2%, respectively. Of note, in group A, 7 of 11 patients, and in group B, 6 of 7 patients who exhibited disease progression did so after discontinuation of imatinib following 2 years of treatment.

| TABLE 33-3: MULTI-INSTITUTIONAL TRIALS EVALUATING NEOADJUVANT OR ADJUVANT IMATINIB IN THE PERIOPERATIVE MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS (GISTS) |
McAuliffe and colleagues from M.D. Anderson Cancer Center (MDACC) reported results of a phase II, single-institution trial investigating neoadjuvant imatinib in patients with primary and metastatic GIST ≥1 cm. With a
hypothesis that molecular mechanisms of imatinib efficacy are initiated prior to detectable histopathologic cytoreduction, 12 patients with primary GIST and 5 patients with metastatic GIST were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg/day) followed by 2 years of postoperative adjuvant imatinib. In addition to a radiographic response in all patients within the first week of treatment, tumor cell apoptosis was increased in treated patients when compared to treatment-naïve patients, and this also correlated with duration of treatment.

The German APOLLON study is a prospective, phase II, open-label trial that investigated the overall tumor response and progression rate of disease in patients with locally advanced, non-metastatic KIT- or PDGFRA-positive GISTs. Patients received neoadjuvant imatinib (400 mg/day) for 6 months and no postoperative adjuvant therapy. Thirty-four patients underwent resection, 30 with a R0 resection. Results demonstrate that when compared to imaging performed after the first 2 months of neoadjuvant treatment, the operation required was significantly downstaged in the majority of patients after 6 months of neoadjuvant imatinib treatment.

The largest retrospective study to date comprises 161 patients pooled from 10 European Organization for Research and Treatment of Cancer (EORTC) and Soft Tissue and Bone Sarcoma Group (STBSG) databases. All patients were treated with neoadjuvant imatinib (400 mg/day) until a “maximal response” was achieved, defined as two consecutive CT scans showing stable disease (median 40 weeks; range 6-190 weeks). A R0 resection was obtained in 83% of patients and adjuvant therapy was continued in 56% of patients for at least 1 year. Five-year disease-free survival (DFS) was 65% and 5-year OS and DSS from the start of imatinib therapy were 87% and 95%, respectively.

Neoadjuvant trials of advanced GIST have demonstrated that maximal radiographic response to imatinib generally required 6 to 9 months of treatment. Thus, the optimal preoperative imatinib regimen may be 6 months or more as long as continued radiographic response is observed (Fig. 33-8).
FIGURE 33-8  Patient with primary gastric GIST before (A) and after (B) 9 months of neoadjuvant imatinib. Neoadjuvant therapy resulted in dramatic tumor shrinkage.
A recent retrospective review by Tirumani and colleagues identified the timing of the earliest, best, and plateau response to neoadjuvant imatinib. Of 20 patients receiving neoadjuvant imatinib (400 mg/day), 16 showed a partial response and 4 showed stable disease during a median treatment course of 32 weeks. The best response to neoadjuvant imatinib was an 83% reduction in volume at a median interval of 28 weeks, irrespective of tumor size and location. Ten patients who reached a plateau response did so at a median interval of 34 weeks, with the best response noted at 19 weeks. The authors conclude that once a tumor response reaches a plateau, a patient should be considered for surgery, as further tumor response is unlikely and thus the scope of the resection is likely not to change further.

Current NCCN guidelines recommend initial starting dose of imatinib at 400 mg/day, with consideration of 800 mg/day for patients with KIT exon 9 mutation to improve response rates. Monitoring of response to neoadjuvant imatinib by PET-CT or CT is completed at 3-monthly intervals until there is stable disease on two consecutive scans or when progression is documented despite escalation of imatinib dose (plateau response). These recommendations lack supporting evidence and do not provide an optimal time frame for surgical resection. Decisions to proceed to surgery or remain on imatinib should be made jointly by surgeon and medical oncologist using PET-CT or CT scan as evidence of stability, response, or progression. If surgical therapy is planned, imatinib may be stopped just prior to surgery and reinitiated with the resumption of gastrointestinal function.

At present, there have been no trials specifically addressing the use of other TKIs including sunitinib malate (SU11248, Sutent, Pfizer, Inc.) or regorafenib (Stivarga, Bayer) in the neoadjuvant setting. Although data from the metastatic setting and algorithms for progressive use of TKIs are applied to locally advanced tumors, the isolated and/or additive effect of these second- and third-line agents on DFS and/or OS is yet undefined.

**Adjuvant Therapy for Primary Disease**

The role of adjuvant therapy with imatinib combined with surgical resection of primary disease has been explored in several prospective randomized multiinstitutional trials. The trials tested durations of adjuvant imatinib of 12 months (American College of Surgeons Oncology Group Z9000, ASOSOG
The American College of Surgeons Oncology Group (ACOSOG) trial Z9000 was the first phase II trial to investigate the use of adjuvant imatinib (400 mg/day) for 12 months after complete resection in patients with high-risk GISTs.\textsuperscript{123} High risk was defined as tumor diameter of 10 cm or more, intraperitoneal tumor rupture, or up to four peritoneal implants. At a median follow-up of 7.7 years, RFS rates at 1, 3, and 5 years were 96%, 60%, and 40%, respectively, and OS rates were 99%, 97%, and 83% at 1, 3, and 5 years, respectively. The authors concluded that adjuvant imatinib for 12 months in patients with primary GIST who are at a high risk of recurrence prolongs overall survival when compared to historical controls. However, the optimal duration of adjuvant therapy could not be determined.

In 2009, results from the ACOSOG trial Z9001, the first phase III, randomized, placebo-controlled, multicenter trial were published.\textsuperscript{124} In this trial, 713 patients who underwent resection of a primary GIST ≥3 cm were randomized to receive imatinib (400 mg/day) or placebo for 12 months after surgery. RFS was significantly longer in the imatinib arm compared to the placebo arm in all risk categories (97% vs 83%, \( p = 0.0000014 \)). The trial was stopped early due to encouragingly positive results at interim analysis, with a shortened median follow-up of 19.7 months. Interestingly, once recurrences were observed, the slopes of the Kaplan–Meier survival curves for both treatment arms were similar. This suggests that adjuvant imatinib delays recurrence, but overall disease trajectory remains unchanged. No significant difference in overall survival was observed between the two arms. The results of this study led to the approval of imatinib in the adjuvant setting by the US Food and Drug Administration for GISTs ≥3 cm, but with poor guidance on optimal treatment duration.

The SSG XVIII trial is a phase III prospective, randomized, open-label trial that evaluated 12 versus 36 months of adjuvant imatinib (400 mg/day) following resection of high-risk GISTs.\textsuperscript{126} High-risk GISTs in this study were defined as tumor diameter >10 cm, mitotic count >10/50 HPF, tumor size >5 cm with mitotic rate >5/HPF, or tumor rupture. With a median duration of follow-up of 54 months, patients treated with 36 months of imatinib had a
significantly longer 5-year RFS compared to 12 months of treatment (66% vs 48%, \( p < 0.01 \)). Most importantly, overall survival was found to be significantly better in the 36-month treatment group (92% vs 82%, \( p = 0.02 \)), which was the first time an overall survival benefit associated with the use of adjuvant imatinib was reported. However, there was no difference in DSS.

The Intergroup EORTC 62024 trial is a phase III, randomized, open-label trial comparing 2 years of adjuvant imatinib with observation in patients with intermediate- or high-risk GISTs. Following surgical resection, patients were randomized to receive imatinib (400 mg/day) or observation alone. With a preliminary reported median follow-up of 4.7 years, no significant difference was observed in the 5-year imatinib failure-free survival (\( p = 0.23 \)). However, a subset analysis of patients with high-risk GIST showed a trend in favor of imatinib treatment (\( p = 0.11 \)). RFS at 3 and 5 years was significantly longer in the imatinib treatment group (\( p < 0.001 \)), but there was no difference in 5-year OS.

The PERSIST-5/CSIT571BUS282 trial is a phase II trial examining the use of imatinib (400 mg/day) after complete surgical resection in patients with primary GIST ≥2 cm with a mitotic rate ≥5/50 HPF or non-gastric primary GIST ≥5 cm. Accrual is complete but preliminary results on RFS have yet to be reported.

The results of the Z9001 and SSG XVIII trials led to guideline recommendations of adjuvant imatinib for at least 3 years for patients with intermediate or high risk of GIST recurrence. However, optimal adjuvant imatinib treatment length is still unknown.

Perhaps the most important question is whether administration of imatinib after complete resection of primary disease or after disease recurrence delays time to second- or third-line therapy. In addition, combining the data for sequential targeted medical therapies with more granular data on the behavior of different mutational subtypes lends increasing complexity to this clinical scenario.

**THERAPY FOR ADVANCED DISEASE**

The majority of GIST recurrences occur in the first 5 years following surgical resection. In a pooled analysis of 10 series including 1625 patients undergoing surgical resection in the absence of adjuvant imatinib treatment,
the 5-, 10-, 15-, and 20-year recurrence-free survival rates were 70.5%, 62.9%, 59.9%, and 57.3%, respectively. Up to two-thirds of these patients with a recurrence will have liver metastases and approximately half will have peritoneal disease. Historically, patients with recurrent and metastatic GIST have been treated by a combination of the three traditional cancer therapeutic modalities: surgery, intravenous chemotherapy, and radiotherapy. Surgery may be effective for patients with resectable disease, but disease may recur in as many as 50% of individuals at a median of 24 months. Traditional intravenous chemotherapy (including standard sarcoma regimens employing doxorubicin +/− ifosfamide) and radiotherapy show poor efficacy.

Imatinib Therapy for Recurrent and Metastatic Disease

To date, three TKIs have been approved for the treatment of metastatic GIST: imatinib mesylate, sunitinib malate, and regorafenib. Imatinib is the first-line therapy for advanced (unresectable primary, recurrent, or metastatic) GIST, based on data from international phase I, II, and III trials. The initial report of successful treatment of metastatic GIST in 2001 determined the efficacy and optimal dosing of imatinib. Subsequently, the Intergroup B2222 trial, a phase II, randomized, open-label, multicenter trial that compared imatinib doses of 400 mg/day and 600 mg/day in patients with advanced disease, was completed. With a median follow-up of 63 months, 2 of 147 patients (1.4%) achieved a complete response and 98 of 147 patients (67%) demonstrated a partial response, with no significant difference in response rates between the two doses. There was no difference in PFS and OS between the two groups. Median time to progression was 24 months and median OS was 57 months for all patients.

The subsequent phase III, randomized, open-label S0033 trial compared outcomes of imatinib 400 mg/day to 800 mg/day in patients with advanced GIST. A total of 746 patients were enrolled in this multicenter study with a median follow-up 4.5 years. There were no significant differences in response rates between the two treatment arms. Median PFS was 18 months for patients on 400 mg/day dosing and 20 months for the high-dose arm (p = 0.13) and the median OS rates were 55 and 51 months for lower and higher dosing arms, respectively (p = 0.83). After progression on low-dose imatinib,
33% of patients who crossed over to the high-dose regimen achieved either objective response or stable disease. Subgroup analysis of this crossover group demonstrated a further median PFS of 5 months and an additional median OS of 19 months after dosage increase.

The similarly designed EORTC phase III randomized trial compared daily imatinib 400 to 800 mg dosing. With a median follow-up of 760 days, the 2-year PFS rates were 56% and 50% (p = NS) and 2-year OS rates were 69% and 74% (p = NS) for low- and high-dose regimens, respectively. There was no significant difference in response rates between the two groups.

A meta-analysis combining the results from the EORTC and S0033 trial (MetaGIST) demonstrated a slight advantage in PFS in patients initially treated with the higher, 800 mg/day, imatinib dose (p = 0.17). This PFS advantage was only demonstrated in patients with KIT exon 9 mutations, and that was the only factor predicting benefit from the high-dose regimen in multivariable analysis. There was no significant difference in OS. The PFS curves demonstrated that the majority of the improvement appeared within the first 2 years of high-dose treatment. It should be noted that almost 50% of patients in the high-dose treatment arm required dose reduction within 6 months due to medication intolerance or toxicity.

Based on the results of these clinical trials, the current standard of care for advanced GIST is imatinib starting at a dose of 400 mg/day. Imatinib at 800 mg/day (dosed as 400 mg twice daily) should be considered as starting dose for patients with advanced GIST with a confirmed KIT exon 9 mutation. Correlation of kinase genotype and dose selection has been confirmed by analysis of data from both the S0033 and EORTC trials. Of note, these two studies found that patients with KIT exon 11 mutations are more likely to have a partial response and have a longer PFS than those with a KIT exon 9 mutation or WT GIST.

Once imatinib therapy is initiated for the treatment of advanced GIST, it should be continued indefinitely. The French BFR14 trial was a phase III, randomized, open-label, multicenter trial evaluating the effect of imatinib interruption in patients with advanced GISTs. Patients with nonprogressive disease who were randomized to interruption of imatinib therapy after 1 and 3 years had a much higher rate of disease progression than those who continued therapy. Of those patients randomized to the imatinib continuation treatment arm after 1 year of treatment, progression was noted in
31% of patients compared to 81% in the interruption arm. When imatinib was reintroduced in the interruption arm, 92% responded. Following 3 years of treatment with imatinib, the 2-year PFS was 80% in the continuation group and 16% in the interruption group ($p <0.0001$) after a median follow-up of 35 months. Data presented for interruption of imatinib treatment after 5 years demonstrated that 45% of patients relapsed during the first year of follow-up, whereas no further progression was noted in any patient assigned to the continuation treatment arm ($p = 0.032$). Based on these results, it is clear that imatinib should be continued until disease progression or treatment-related toxicities become intolerable.

A recent phase III, randomized, double-blind, single institution trial was completed to assess the efficacy of imatinib rechallenge in patients who progressed on TKI. After a short median follow-up of 5.2 months, median PFS was 1.8 months with imatinib compared with 0.9 months with placebo ($p = 0.005$). The median PFS improved to 1.7 months in 37/40 patients randomized to the placebo group who crossed over to imatinib treatment. No significant difference, however, in OS was demonstrated between imatinib and placebo groups (8.2 vs 7.5 months, respectively; $p = 0.92$). The authors concluded that in patients with GISTs that are refractory to treatment with all standard tyrosine kinase inhibitors, the disease may continue to harbor clones that are still sensitive to kinase inhibitors, and continued imatinib treatment may slow progression.

**Therapy for Imatinib Resistance**

While imatinib benefits the majority of patients with advanced GISTs, there is a subset of patients who fail to demonstrate an initial response, and/or who progress while on imatinib. Primary resistance is defined as evidence of clinical progression during the first 6 months of imatinib therapy, and occurs in approximately 14% of patients with advanced GISTs. Primary resistance is most commonly seen in patients with WT-GISTs, with mutations involving $KIT$ exon 9, or with a D842V mutation in $PDGFRA$ exon 18. Eventually, most patients develop secondary resistance, which occurs in patients who have been treated with imatinib for longer than 6 months with an initial response who then develop progressive disease. Secondary KIT mutations most commonly occur in $KIT$ exons 13, 14, and 17 and a D842V mutation in
Acquisition of secondary KIT mutations has been shown to confer imatinib resistance by either directly altering the adenophosphate triphosphate (ATP)/drug-binding pocket or by interfering with access to this pocket through conformational changes in the activation loop of the kinase. Other mechanisms of imatinib resistance involve the KIT-dependent and -independent process by KIT gene amplification and complete loss of KIT expression. Resistance is managed by increasing imatinib dose to 800 mg/day or switching to a second- or third-line agent.

Sunitinib is indicated as a second-line therapy for patients with advanced GISTs who progress on or become intolerant to imatinib. Sunitinib is a tyrosine kinase inhibitor that targets KIT, PDGFR, vascular endothelial growth receptor (VEGFR1, VEGFR2, VEGFR3), the ret proto-oncogene receptor (RET), and Fms-like tyrosine kinase-3 receptor (Flt3). A phase III, randomized, placebo-controlled trial evaluated outcomes in patients receiving sunitinib for advanced GISTs after failure and discontinuation of imatinib. Significant improvement in time-to-progression in patients treated with sunitinib was demonstrated when compared to those treated with placebo (27.3 weeks vs 6.4 weeks, respectively; \( p < 0.0001 \)), as well as PFS and OS. Sunitinib in this study was administered for 4 weeks followed by 2 weeks off treatment. A phase II, open-label, single arm study has since evaluated the efficacy of continuous, daily dosing of sunitinib at a dose of 37.5 mg/day. The study reported a complete response rate of 53%, partial response 13%, and 40% achieved stable disease greater than 24 weeks. The median PFS was 34 weeks and the median OS was 107 weeks. Based on these studies, sunitinib is now considered the standard of care in patients who have progressed on or are intolerant of imatinib, and is administered in 37.5 mg daily dosing.

Regorafenib is now approved as third-line treatment in patients with advanced GIST who progress on imatinib and sunitinib. Regorafenib is a tyrosine kinase inhibitor that inhibits VEGF1, 2, and 3; PDGFRB; KIT; RET; fibroblast growth factor receptor (FGFR); and BRAF. The recent phase III, randomized, double-blind, placebo-controlled GRID trial evaluated efficacy and safety of regorafenib in patients with advanced GIST who had evidence of progression after failure of at least imatinib and sunitinib. The median PFS of patients randomized to regorafenib was 4.8 months compared to 0.9 months for the placebo group (\( p < 0.0001 \)). The rate of durable stable disease
lasting for greater than 12 weeks was 52.6% and 9.1% in the regorafenib and placebo groups, respectively. The results of this study led to the approval of regorafenib by the US Food and Drug Administration as the preferred third-line drug for GISTs.

Sorafenib is a tyrosine kinase inhibitor that is selective for KIT, PDGFRB, VEGF (isoforms 1-3), and Flt3, among others, that has shown clinical benefit in retrospective studies and phase II trials in patients who failed other TKIs. The largest retrospective review by Montemurro and colleagues was a multicenter review that included 124 patients treated with sorafenib (400 mg/day) as a third- or fourth-line treatment for advanced GIST. Partial response was observed in 10% of patients and stable disease in 57%. Median PFS was 6.4 months and median OS was 13.5 months. Preliminary results for a multicenter phase II trial also showed similar beneficial outcomes. Of the 38 patients enrolled, 13% demonstrated a partial response and 55% of patients experienced stable disease over a median follow-up of 31 months. Median PFS was 5.2 months and median OS was 11.6 months, with a 1-year OS of 50%. While these studies suggest that sorafenib is a reasonable third- or fourth-line treatment, additional data from phase III clinical trials is needed to clearly define its role.

Nilotinib is a second-generation TKI that was originally designed for the treatment of chronic myelogenous leukemia due to its activity against bcr-abl. Nilotinib has additional activity against PDGFRA and KIT and has been shown to improve outcomes in patients with imatinib- and sunitinib-resistant GISTs. The use of nilotinib alone or in combination with imatinib was initially shown to be tolerable with clinical activity in imatinib-resistant GISTs in a phase I trial. Of the 52 enrolled patients, 38 patients exhibited a stable disease and 2 patients a partial response. A phase III, randomized, open-label trial did not show an improvement in PFS with a median of 109 days in the nilotinib arm and 111 days in the best supportive care control arm. It is important to note that 93% of patients in the control arm were receiving imatinib or sunitinib as part of best supportive care. In the post hoc subset analyses, patients receiving nilotinib after progression on imatinib and sunitinib demonstrated a significantly longer OS with a median of 405 days versus 280 days (p = 0.02). A multicenter, phase III, randomized trial is currently ongoing to investigate the efficacy and safety of nilotinib versus imatinib as a first-line treatment in patients with advanced GIST.
Multiple additional tyrosine kinase inhibitors are currently under investigation including dasatinib, vatalanib, mastinib, dovitinib, pazopanib, and crenolanib. Crenolanib is of particular interest as it is a kinase inhibitor of PDGFRA and has been found to be 135-fold more potent than imatinib against the PDGFRA D842V mutation in vitro. A multicenter phase II trial investigating the use of crenolanib for treatment of PDGFRA D842V-mutant GIST is ongoing.

In addition, other non-TKI agents are being investigated, including panobinostat, heat shock protein-90 inhibitors, and mTOR inhibitors such as everolimus. Investigators are also exploring the role the immune response plays in the antitumor effects of imatinib in GIST. Using a mouse model of spontaneous GIST, investigators have found that imatinib therapy results in activation of CD8+ T cells and induces regulatory T cell apoptosis within the GIST tumor by reducing tumor cell expression of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (Ido). Addition of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade potentiated the effects of imatinib in this model. This immunotherapeutic approach with the combination of imatinib and CTLA-4 blockade is a promising approach in improving outcomes in patients with advanced GIST.

**Cytoreductive Surgery**

Cytoreductive surgery for advanced or metastatic disease is an accepted practice for disseminated solid tumors originating in the colon, appendix, ovary, and testicle. With the advent of targeted TKIs prolonging DFS and OS, clinicians are exploring the benefits of aggressive cytoreductive surgery in patients with advanced GIST. Three biologic tenets support this approach. First, the majority of patients experience durable periods of PR or SD on imatinib, lasting months to years. Second, pathologic complete responses are rare, noted in fewer than 5% of patients. Third, response to imatinib is not maintained indefinitely; the median time to progression due to the development of secondary resistance is 18 to 24 months. Once drug resistance develops, disease progression may be either limited (progression at one site of tumor, with other tumor deposits showing ongoing response to TKI) or generalized (progression at more than one site). Given these patterns of tumor behavior, cytoreductive surgery has several
purported biologic benefits. Surgery may reduce the burden of clonal variability in the tumor population and may prevent the formation of drug-resistant clones. This is turn may render the individual’s remaining tumor burden again responsive to first- or second-line therapies. Furthermore, cytoreductive surgery may have a role in reducing symptoms and the development of complications such as perforation and bleeding. However, challenges lie in determining the optimal time for surgical intervention and the extent of surgery required to achieve meaningful clinical changes in outcomes.

The goal of cytoreductive surgery is to safely perform a macroscopically complete (R0 or R1) resection. Unfortunately, only 12% to 23% of patients with advanced GISTs on imatinib are considered surgical candidates.\textsuperscript{170,171} The integration of surgery with multiple new emerging medical therapies is evolving.

There have been no fully completed randomized controlled trials comparing TKI therapy and cytoreductive surgery with medical therapy alone in the setting of advanced GISTs. Phase III trials to answer this question were designed and/or initiated in China, Europe, and the United States but remain unsuccessful due to poor accrual. Further phase III trial attempts are unlikely to occur. The Chinese group published results from their initially accrued patients with 19 patients in the surgery and imatinib arm and 22 patients in the imatinib-alone (400 mg/day) arm.\textsuperscript{172} Patients in the surgery were treated with 3 to 12 months of medical therapy. Two-year PFS was 88.4% and 55.7% in the surgery with imatinib and imitinib-alone arms, respectively ($p = 0.089$), suggesting no significant difference with these early and poorly powered results. However, several single-institution retrospective studies have documented promising PFS and OS rates following extensive cytoreductive surgery in patients with advanced GIST pretreated with TKI therapy.\textsuperscript{168–171,173,174}

A study from the Brigham and Women’s Hospital/Dana-Farber Cancer Institute (BWH/DFCI) evaluated outcomes in 69 patients who underwent cytoreductive surgery while receiving kinase inhibitors.\textsuperscript{169} In this study, following surgery, there was no evidence of disease in 78%, 25%, and 7% of patients with stable disease, limited progression, and generalized progression, respectively ($p <0.0001$). For patients with stable, limited progression, and generalized progression, the 1-year PFS was 80%, 33%, and 0%,
respectively, and 1-year OS was 95%, 86%, and 0%, respectively. The authors concluded that patients with stable or limited disease progression are more likely to benefit from debulking procedures than those with generalized progression, particularly if an R0 or R1 resection is completed or tumor burden is reduced such that no individual nodule greater than 1 cm in diameter remains.

A study from Memorial Sloan Kettering Cancer Center (MSKCC) found similar results when evaluating outcomes following imatinib therapy and cytoreduction for advanced GISTs. Patients with responsive disease, defined as having had a partial response or stable disease on kinase inhibitor therapy, had a 2-year PFS of 61% and a 2-year OS of 100%. Those patients with focal resistance or radiologic evidence of growth in one tumor progressed after surgery at a median of 12 months and had a 2-year OS of 36%. Patients who exhibited growth in more than one tumor progressed at a median of 3 months and had a 1-year OS of 36%. The majority of patients underwent liver resection (43%), and 68% of patients required resection of peritoneal metastases without resection of a major organ, which is similar to the BWH/DFCI study.

These results support the role of cytoreduction surgery in a subset of carefully selected resectable patients with continuation of TKI up to the surgery and also postoperatively. However, these series alone do not establish the superiority of surgery plus TKI over medical therapy alone. In light of current data, surgery should not be the first-line treatment for advanced GISTs, barring an impending emergency. These patients should be treated with imatinib for a minimum of 6 months prior to consideration of surgery. Patients with disease that is stable or with limited progression should be individually assessed by a team of GIST specialists to determine if as they may benefit from prolonged PFS or OS following cytoreductive surgery (Fig. 33-9). Patients with generalized progression have not been shown to benefit from cytoreductive surgery and are best treated nonoperatively (Fig. 33-10). If surgery is not a viable option, symptomatic patients or patients with limited progression may be considered for other targeted but less invasive therapies such as radiofrequency ablation or (chemo)embolization for liver disease, radiation for isolated bony metastases, or transition to other protocol-based therapies.
FIGURE 33-9  Patient with duodenal GIST metastatic to the liver (arrows)
before (A) and after (B) eight months of imatinib, demonstrating partial response to therapy. The patient underwent resection of his intact primary disease, a right hepatectomy, and wedge resection of a left hepatic lesion.
**FIGURE 33-10** Patient with unresectable metastatic GIST (A and B). Therapy with imatinib failed to control growth of the disease. The patient underwent a palliative debulking to relieve proximal gastric obstruction, but the resection as anticipated was macroscopically incomplete.

**SURVEILLANCE**

There is no established prospective data to define optimal surveillance for patients with GISTs. However, follow-up schedules have been developed based on evidence that most recurrences occur within the first 5 years following surgery. NCCN guidelines recommend patients who have undergone surgical resection of a GIST undergo contrast-enhanced surveillance CT imaging of the abdomen/pelvis every 3 to 6 months for the first 3 to 5 years, then annually thereafter. The ESMO guidelines recognize that follow-up schedules differ across institutions and that the risk of recurrence should guide the follow-up schedule. High-risk patients should undergo routine follow-up with CT scan every 3 to 6 months for 3 years, every 3 months for 2 years (closer follow-up after cessation of adjuvant imatinib therapy), every 6 months until 5 years, and then annually until 10 years. For low-risk tumors, patients require less rigorous follow-up and could have CT imaging every 6 to 12 months for 5 years. Very low-risk GISTs probably do not even need to be followed. CT imaging is the preferred modality, as it is more readily available than MRI or FDG-PET-CT scan imaging; however, these modalities can be considered when CT findings are inconclusive. Routine imaging of the chest or brain is unnecessary.

**CONCLUSIONS**

The principal and only potentially curative treatment for GIST is surgery. However, recurrences are common. Historically, survival in the setting of recurrent or metastatic disease has been poor. However, TKI therapy has dramatically transformed the natural history of this disease, and the role of mutational analysis in the type and dose of TKI administered is actively evolving. The role of imatinib has been expanded in patients with primary GIST to include use in the neoadjuvant setting and adjuvantly following complete macroscopic and microscopic resection in intermediate- to high-risk
patients\textsuperscript{177} (Fig. 33-11). Ongoing studies will address the optimal length and dose of these therapies, define the subset of candidates most likely to benefit, and determine the long-term impact on OS.

**FIGURE 33-11** Schema for management of primary and advanced gastrointestinal stromal tumor.

TKIs are the mainstay of treatment for locally advanced, recurrent, and metastatic GIST. However, cytoreductive surgery may be considered in a subset of patients with advanced disease, although superiority over medical therapy alone is uncertain. Future work aims to add to the understanding of the complex integration of an individual’s molecular tumor characteristics with surgery and targeted therapy. With an improved understanding of this landscape, strategies can then be fashioned to battle drug-resistant GISTs and improve survival for these patients.

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PERSPECTIVE ON GASTROINTESTINAL STROMAL TUMORS

Michael J. Cavnar • Ronald P. DeMatteo

INTRODUCTION

In Chapter 33, Drs. Look Hong and Raut review gastrointestinal stromal tumor (GIST). Historically, metastatic GIST carried a median survival of 12 months, but this has improved to 5 years with the introduction of tyrosine kinase inhibitors (TKIs)\(^1\,^2\). The landmark finding of the effectiveness of imatinib in GIST has transformed a disease for which little treatment beyond surgery existed into a chronic disease for which multimodality therapy can give patients prolonged survival with good quality of life and possibly even cure. Following the success of imatinib in GIST, the paradigm of targeted molecular therapy has rapidly expanded, with US Food and Drug Administration (FDA) approval of orally available targeted molecular therapy agents for multiple targets in multiple solid tumors. Initial success with targeting tyrosine kinase receptors in non–small-cell lung cancer (EGFR and later ALK) and renal cell carcinoma (VEGFR) has now been broadened to
include approval of drugs for breast cancer, colorectal cancer, thyroid cancer, soft tissue sarcoma, and pancreatic neuroendocrine tumor. In some instances, just 1 or 2 kinases are targeted, whereas in others, multiple kinases are inhibited. Additional available agents are now also widely used for targets downstream of tyrosine kinases, including BRAF in melanoma; mTOR in breast cancer, angiomyolipoma, and pancreatic neuroendocrine tumors; CDK4/6 in breast cancer; PARP in ovarian cancer; and Hedgehog in basal cell carcinoma. While experience gained in the treatment of GIST has paved the way for the introduction of targeted therapy in many other cancers, it has also taught us valuable lessons as to complex issues that may arise. The simplicity of targeting KIT or PDGFRA in GIST has turned out to be far more complex than initially thought, with response to therapy dependent on the specific mutation and the nearly inevitable development of secondary mutations and other mechanisms of resistance in advanced and recurrent disease.

While molecular therapy is highly effective, it is important to recognize that surgery remains the only chance for cure in patients with GIST. We now know from the placebo arm of the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial that 70% of patients with GISTs ≥3 cm appear to be cured by surgery with 74 months of follow-up. Given the diverse anatomic locations of primary and metastatic disease, a variety of technical issues must be mastered for appropriate and safe treatment of GIST. Although surgical resection is the central component of treating GIST with curative intent, the surgeon treating GIST must also become knowledgeable in 3 key elements of the molecular therapy for this disease, which we highlight here: (1) appropriate patient selection and duration of neoadjuvant therapy; (2) adjuvant therapy in an increasingly well-defined subset of intermediate- and high-risk patients; and (3) surgical resection in well-selected patients with recurrent or metastatic disease.

**SPECIFIC SURGICAL ISSUES**

For the surgeon planning to resect a GIST, it is important to understand a number of unique surgical principles. GISTs are extremely friable, especially after neoadjuvant imatinib, and thus may rupture if not handled with great care. Tumor rupture must be avoided as it may lead to early peritoneal
recurrence and is known to worsen outcome. As such, tumor handling during laparoscopy is best achieved by minimal direct contact with the tumor, and once resected, the tumor must be removed via a retrieval bag to prevent tumor seeding. GISTs are particularly vascular, with the potential for significant blood loss if the extensive venous and arterial collateral vessels are not carefully dissected and ligated. While GISTs do not typically invade into adjacent organs and instead push them aside, any organ adherent to a GIST should be removed at least partially en bloc.

Since GISTs arise in diverse locations, with highest frequency in the stomach followed by small intestine, rectum, and occasionally other sites, site-specific considerations are numerous. Laparoscopic (and possibly robotic) surgery is appropriate in each of these sites for small- to medium-sized tumors if the surgeon has adequate expertise and the appropriate equipment. When these tumors are small and have a low mitotic rate, cure by surgery alone is possible, particularly for gastric GISTs. During laparoscopic exploration, exophytic gastric tumors are readily identified, especially along the greater curvature and anterior stomach. Tumors that grow into the stomach lumen instead of exophytically can be identified by intraoperative endoscopy, or by filling the stomach with water and using laparoscopic ultrasound, although this is rarely necessary. Posterior gastric tumors are usually still amenable to minimally invasive resection but require extensive mobilization of the stomach, which is further facilitated by retracting the left lateral segment of the liver to the right. Formal anatomic gastrectomy is typically not required; rather, partially gastrectomy with a 1-cm margin is adequate.

Partial gastrectomy is frequently possible using surgical staplers, unless doing so will lead to unacceptable compromise of the gastric lumen. In this case, a gastrotomy is made and the tumor resected with a 1-cm margin using cautery, followed by hand-sewn closure of the defect. For GISTs arising from the gastroesophageal junction (GEJ), we prefer open surgery, especially for posterior tumors. We typically remove these tumors by gastrotomy and hand-sewn closure; however, if staplers are used, a bougie should be placed in the esophagus to avoid narrowing the GEJ. Total gastrectomy is rarely required for massive gastric tumors, and the postoperative complications should be considered and discussed with the patient preoperatively. Such large tumors may be intimately associated with other organs including the distal pancreas, spleen, and even the splenic flexure of the colon, possibly requiring en bloc
resection. When the extent of the tumor is recognized preoperatively, neoadjuvant imatinib (as discussed below) is highly recommended and may result in organ preservation.

The small intestine is the next most frequent site of primary GIST. Jejunal and ileal GISTs are readily removed laparoscopically, unless very large. They are easily identified by systematically running the small bowel from the ligament of Treitz to the terminal ileum. Duodenal GISTs are perhaps the most complex to deal with. Tumors located in the second portion of the duodenum may require a pancreaticoduodenectomy, unless small and arising from the lateral wall. In that case, local resection may be possible either using primary closure of the defect or reconstruction with a Roux-en-Y jejunal limb. GISTs in the third or fourth portion of the duodenum can be resected after appropriate mobilization and reconstructed either with a direct anastomosis to jejunum or with closure of the distal duodenum and creation of a Roux-en-Y limb of jejunum to the lateral second portion of the duodenum. For a duodenal tumor that is larger than a few centimeters, neoadjuvant imatinib should be considered if it may reduce the extent of the operation required.

GIST rarely arises in the colon, but rectal GISTs make up approximately 5% of primary tumors and thus deserve discussion. Akin to adenocarcinoma of the rectum, an organ-preserving neoadjuvant approach should be employed. This may allow avoidance of abdominoperineal resection and permanent colostomy. Likewise, it may allow local transanal resection for very distal tumors.

Many patients with GISTs already have a tissue diagnosis by the time of referral. However, for tumors with a classic radiologic appearance, biopsy may not be necessary, although the patient should be counseled preoperatively that other tumors such as Schwannoma, leiomyoma, or even ectopic pancreas are possible. Biopsy should be performed if identification of a benign tumor may avoid an otherwise morbid resection, such as an esophagectomy for a GEJ tumor. Likewise, if neoadjuvant therapy is being considered for a large tumor, biopsy is generally recommended to confirm the tumor is a GIST.

Given that GIST only rarely spreads to lymph nodes, it is not necessary in any of the typical sites to perform a lymphadenectomy, unless preoperative imaging indicates lymphadenopathy (in which case one should suspect the tumor is likely not a GIST) or enlarged nodes are palpated at operation.
NEOADJUVANT THERAPY

We now have considerable experience with neoadjuvant imatinib therapy to improve resectability of locally advanced primary tumors and recurrent/metastatic disease. Patient selection for neoadjuvant therapy is based on several factors. Size is not an absolute indication, especially if primary resection is feasible (e.g., a large primary jejunal or ileal tumor). However, if multivisceral resection will be required based on size, then neoadjuvant treatment should be considered. Neoadjuvant therapy may also allow a laparoscopic approach instead of laparotomy. Location at the GEJ, duodenum, or rectum often warrants neoadjuvant therapy with tumors larger than a few centimeters. Recurrent tumors and metastases that are also larger than a few centimeters also benefit if reduction in size or vascularity will facilitate less morbid resection.

While the neoadjuvant strategy is widely employed for other cancers such as esophageal, gastric, and rectal cancer, unlike cytotoxic chemotherapeutic agents used in those diseases, which have to be stopped many weeks before surgery, imatinib (and other TKIs such as sunitinib, regorafenib, and others) can be stopped a day or 2 prior to surgery without concern for adverse effect on wound healing or immune suppression. Response Evaluation Criteria in Solid Tumors (RECIST) are used to assess response in most cancers, but these criteria do not work well in GIST, where the tumor may swell temporarily after treatment. Instead, the Choi criteria, which incorporate density and size, are useful to detect early treatment response. Generally, we perform a computed tomography (CT) 2 to 4 weeks after starting imatinib to check for tumor response. Because size is not the best indicator of response, it is important that the surgeon personally review the images, as the radiologist may not report changes in tumor density. The optimal length of imatinib therapy remains to be determined. After initiation of therapy, it is our practice to repeat scans at 3 and 6 months, and attempt resection at 6 to 8 months if there is no progression of disease. Meaningful shrinkage is unlikely past this time period.

While prospective randomized trials of neoadjuvant therapy compared to immediate surgery are lacking, the authors cite a small but growing literature of retrospective studies and single-arm or nonplacebo controlled prospective trials showing that the neoadjuvant strategy allows R0 resection in the majority of patients with well-selected locally advanced primary tumors or
recurrent/metastatic disease. Although some of these studies report survival data, without a matched comparison group, the value of these data is uncertain. Still, neoadjuvant therapy may improve organ preservation independent of progression or survival, affecting morbidity and quality of life. Given that the patients who warrant neoadjuvant therapy are typically at high risk of recurrence, continuation of adjuvant imatinib therapy after surgery is prudent, although this has not been rigorously studied. After surgery, imatinib and others TKIs can be resumed once the patient is tolerating a regular diet and having bowel function.

**ADJUVANT THERAPY**

As covered by the authors, high-level evidence now supports prolonged adjuvant therapy with imatinib after resection for a subset of intermediate- and high-risk primary, localized GISTs. The initial results of a prospective randomized phase III trial of 1 year of adjuvant imatinib compared to placebo (ACOSOG Z9001) showed prolonged recurrence-free survival (RFS) with a median follow-up of 19.7 months, leading to FDA and European Medicines Agency approval of imatinib in GIST.\(^6\) We subsequently reported long-term follow-up (median, 74 months) from this cohort, which demonstrated persistence of prolonged RFS.\(^4\) This result was evident even without censoring placebo-treated patients who crossed over into the imatinib arm. This is remarkable given that the patients only received 1 year of therapy and the study included many patients with tumors that we now know were at low risk for recurrence. However, 1 year of imatinib was not enough to prevent recurrence, as patients in the imatinib arm began to experience recurrences after discontinuation of the drug. Another large prospective randomized phase III trial (SSG XVIII) showed superior RFS with 3 years compared with 1 year of adjuvant imatinib.\(^7\) This study showed slight improvement in overall survival (OS), but not disease-specific survival (DSS). In general, OS benefit in these studies has been difficult to prove given the low event rate of death from disease and, more importantly, because imatinib is a highly effective salvage therapy.

Study of extended therapy is ongoing. PERSIST-5 is a single-arm phase II trial of 5 years of imatinib in patients at high risk of recurrence from primary GIST including any site \(\geq 2\) cm with \(\geq 5\) mitoses/50 high-power fields (HPFs)
or any nongastric GIST ≥5 cm. At a planned 3-year interim analysis, of 91 eligible patients, only four (4%) had experienced recurrence. Of those 4 patients, 3 had discontinued the drug prior to recurrence and 1 was found to have an imatinib-resistant PDGFRA mutation. Thus, extended adjuvant therapy in high-risk patients appears appropriate, possibly indefinitely, in absence of progression or significant adverse effects. It is our practice to discuss with high-risk patients the goals of care; if the goal is to prolong RFS, understanding that OS and DSS may not be affected, we prescribe chronic imatinib therapy.

Long prospective follow-up of the ACOSOG Z9001 cohort allowed detailed analysis of treatment effect stratified by specific mutation. Surprisingly, the improvement in RFS was only seen in patients with KIT exon 11 deletions, but not exon 11 insertions or point mutations. RFS was not improved in patients with PDGFRA mutations, KIT exon 9 mutations, or wild-type tumors. That the non–exon 11 groups showed limited response is not surprising. The majority of PDGFRA mutations were D842V, which is known to be imatinib-resistant. There were too few non-D842V PDGFRA mutations to make a conclusion about RFS in that group. The small group of KIT exon 9 mutants had equivocal outcome; however, they may have required higher dose imatinib, akin to metastatic disease. Similarly, the small wild-type group, which was not further broken down but typically comprised of SDH, BRAF, NF1, RAS, and other mutations, did not show improved RFS. Still, it was not anticipated that exon 11 insertions and deletions would not show a benefit. Further prospective study will be needed to validate these findings. Nevertheless, it is increasingly clear that molecular stratification will be an important part of selecting patients for therapy.

Despite meticulous surgical technique and R0 resection, many patients will develop tumor recurrence. Using tumor size, location, and mitotic rate, we developed a nomogram to estimate the RFS for patients after resection of primary GIST (http://www.mskcc.org/mskcc/html/98103.cfm). This nomogram has since been validated by a second group in a cohort of 289 patients and had superior predictive accuracy compared to National Institutes of Health and Joensuu criteria. Results obtained from this nomogram can help the surgeon discuss postoperatively with the patient whether adjuvant imatinib therapy would be appropriate. As the influence of specific mutations on imatinib sensitivity is clarified, we will update the nomogram to further
assist in selecting patients for adjuvant therapy or close observation.

**SURGERY FOR METASTATIC GIST**

For metastatic or recurrent GIST, treatment with imatinib has a proven survival benefit and is the standard of care. However, in well-selected patients with limited disease, we and others have advocated surgery when all residual disease can be removed. The authors do cite retrospective series including one from our institution that indicate that resection in patients with TKI-responsive disease have higher progression-free survival (PFS) and OS compared to those with focal resistance or generalized progression on therapy. However, these studies are limited by selection and lead time bias. Several trials to resolve this have been limited by poor accrual, and as cited by the authors, results from initial accrual in a Chinese study (although vastly underpowered) show a trend toward improved PFS that approaches significance. While the true benefit of surgery in recurrent/metastatic GIST remains unproven, in the absence of randomized data, it seems reasonable to perform surgery for metastatic GIST in well-informed patients when the disease has responded to TKIs and complete resection can be achieved. This is supported by the fact that patients with metastatic disease treated with imatinib alone develop progression at a median of 24 months through secondary mutations; thus, R0 resection, if possible, seems prudent. In addition, with appropriate close follow-up of patients after resection of a primary GIST that is high risk, recurrent disease will now frequently be identified early when it may be amenable to resection. After R0 resection of metastatic or recurrent disease, patients should be continued on appropriate TKI, likely indefinitely. For patients with unresectable metastatic disease, second- and third-line TKIs show some effect; however, the benefit is less due to emergence of further resistance. This highlights our need for alternate treatment strategies including immunotherapy, which has substantial scientific rationale in GIST. Indeed, a phase I trial of imatinib plus ipilimumab (anti-CTLA4) in metastatic GIST is ongoing at our institution.

**REFERENCES**


HISTORICAL PERSPECTIVE

The earliest recorded operations on the stomach were performed for penetrating injuries. In the late 1800s, experimental studies in the surgical laboratories of Billroth confirmed the feasibility of removing the pylorus, a concept developed by Michaelis in the early part of that century. In 1881, Rydygier performed the first successful pylorectomy, and in 1884 he performed the first gastroenterostomy. Both of these operations were performed for complications of benign peptic ulcer disease. In 1881, Billroth performed the first successful pylorectomy for malignancy. In this case, the duodenum was anastomosed to the lesser curvature of the stomach and the greater curvature was oversewn. The patient initially did well but died from disseminated abdominal carcinomatosis 4 months later. In 1885, Billroth performed a resection of a large pyloric carcinoma, using an anterior gastrojejunostomy for the reconstruction. In subsequent years, Billroth, his
students, and others devised several approaches to gastroduodenal and gastrojejunal reconstruction.\textsuperscript{1–3} Following popularization of gastrojejunostomy for reconstruction after gastric resection or palliation of unresectable gastric malignancy, surgeons were confronted with early complications such as bleeding, anastomotic leak, intestinal obstruction, and late complications such as stomal ulceration, bilious vomiting, afferent and efferent limb obstructions, and dumping.\textsuperscript{4,5} At present, these problems remain only partially understood and controllable.

Pyloroplasty was initially devised by Heineke for treatment of congenital hypertrophic pyloric stenosis, and the results were poor. Jaboulay’s side-to-side anastomosis of the distal greater curvature and duodenum in 1892 and the Faience extension of this anastomosis to include the pylorus itself were subsequently refined by Kocher. Kocher improved the technical ease of the operation by including a mobilization of the duodenum from its lateral peritoneal attachments. The first pyloromyotomy was performed for this lesion in 1912 by Ramstedt.

In the early part of the 20th century, a dramatic rise was observed in the incidence of duodenal ulceration. A period of intense clinical and laboratory investigation from 1920 through 1940 led to the recognition that surgically performed vagotomy could reduce gastric acidity under resting conditions and in response to luminal and humoral stimuli. The use of vagotomy for patients with complications of ulcer disease was pioneered by Latarjet, who reported 24 such cases in 1922. Latarjet himself recognized that vagotomy might lead to delayed gastric emptying and had added a drainage procedure, gastrojejunostomy. Confusion regarding the role of delayed gastric emptying in the pathogenesis of peptic ulcers, however, led many surgeons away from vagotomy and drainage as a treatment for recurrent peptic ulceration. It remained for Dragstedt and his colleagues at the University of Chicago to resurrect this concept in the 1940s.\textsuperscript{5} Subsequently, Farmer, Smithwick, and others introduced the combination of truncal vagotomy (TV) and hemigastrectomy, an operation that also removed the gastrin-producing antral mucosa.\textsuperscript{3} In the 1950s, Harkins’ group in Seattle began to evaluate forms of vagotony that left intact the celiac and hepatic branches (proximal selective vagotony), along with or in combination with the preservation of vagal motor branches to the antrum (highly selective vagotomy [HSV] or parietal cell vagotomy). These modifications arose from an appreciation of the contributions of antral motility to proper digestion as well as improved
understanding of specific postvagotomy complications such as dumping and diarrhea. The popularization of HSV is largely attributable to the efforts of Johnston, Goligher, Amdrup, and others, who in the 1960s and 1970s demonstrated the feasibility of obtaining ulcer recurrence rates as low as those of conventional TV without the incidence of dumping and diarrhea that was associated with TV with drainage or gastrectomy. It is worth noting that surgeons have done more than developing new and interesting operative approaches to acid peptic disease. They have played a major role in advancing current concepts of pathophysiology in ulcer disease and recurrence, and in understanding the physiological consequences of ulcer treatments, both medical and surgical.

**VAGOTOMY**

Even though the increasing use of medications that inhibit gastric acid secretion, such as proton pump inhibitors, has made elective antisecretory operations essentially nonexistent, these medications remain part of the surgeon’s armamentarium in dealing with patients who remain refractory to maximal medical therapy for ulcer disease, and in some selected cases for patients with ulcer perforation and bleeding. To understand the importance of the technical details in the execution of antisecretory operations, it is necessary to fully appreciate the anatomy of the vagus nerve and the gastric microvasculature, as well as the physiology of acid secretion, mucosal barrier function, and gastric motility, which are expanded upon in the following text.

**Tests of Vagal Control of Acid Secretion**

Historically, vagal control of acid secretion has been assessed by measuring acid secretion in response to various stimuli. Acid secretion can be measured directly by the placement of a tube into the stomach, through which gastric juice is aspirated and the titratable acidity is measured by adding known quantities of 0.1 N NaOH. Gastric output is measured at baseline and after stimulation with pentagastrin or sham feeding. Measurements of gastric acid output pre- and post-vagotomy operations can be measured to assess the efficacy of vagotomy. Acid secretion also can be assessed semiquantitatively, using pH-sensitive dyes, such as Congo red, that coat the
mucosa and turn color when acid is being secreted from the gastric glands.\textsuperscript{10,11} Although the former analytic methods permit accurate and quantitative assays of secretory capacity before and after the operation, the latter colorimetric methods can provide relatively rapid means of assessing secretory capacity of the stomach during the operation itself. These tests are rarely used today with the increasing use of medications that inhibit gastric acid secretion such as proton pump inhibitors and the consequent rarity of performing elective antiulcer gastric acid-reducing operations.

**Vagal Regulation of Gastric Motility and Emptying**

As stated by Professor David Johnson in a previous edition of this book, “… Only when one fully understands the physiologic rationale of highly selective vagotomy will be one sufficiently motivated to do it well.” This statement was made not in reference to the innervation of parietal cells that secrete HCl, but to the neural regulation of gastric motor function and emptying. The vagus dominates the motor activity of the normally functioning stomach in three ways. First, it mediates receptive relaxation and gastric accommodation; that is, the relaxation of the gastric fundus when intraluminal pressures in the proximal esophagus and stomach are increased by the presence of chyme. Second, the vagus mediates increases in antral myoelectrical activity that result from distention of the proximal stomach by chyme. Third, the vagus appears to mediate coordination of pyloric emptying with antral myoelectrical activity in response to changes in proximal gastric motor activity, and perhaps in response to changes in composition and pH of duodenal content.\textsuperscript{12}

It should be recognized that while truncal or selective vagotomy interrupts the vagal pathways to the antrum and pylorus, all three forms of vagotomy (truncal, selective, and highly selective) abolish receptive relaxation and gastric accommodation. It has been claimed that in the absence of pyloric scarring or stenosis, vagotomy only temporarily impairs gastric emptying. This rationale has been used to justify combinations of selective and relatively nonselective approaches, such as a posterior truncal and anterior highly selective (or anterior seromyotomy) vagotomy. Such arguments become important in thinking about potential adverse consequences of laparoscopic approaches to the vagus and the need for, and choice of, drainage procedures. The assumptions that antral/pyloric coordination will
return after truncal vagotomy or that gastric emptying after pyloromyotomy is as good as that after pyloroplasty now seems valid.\textsuperscript{13–15} In addition, the spectrum of complications following such mixtures of approach has now been characterized and is not substantially different than those reported in symmetric operations.\textsuperscript{15,16} Nevertheless, for open or laparoscopic procedures, it is advisable to use the same caution in utilizing mixtures of approach or dispensing with drainage procedures after truncal or selective vagotomy.

Open Approaches to the Vagus

PATIENT POSITION, INCISIONS, AND EXPOSURE

To perform a complete vagotomy, access to the upper part of the stomach and lower esophagus is crucial. It is helpful for the operating surgeon, standing on the patient’s right, to wear a headlight. When access to the duodenum is required, as in a gastrectomy, excellent exposure is available through a chevron incision. However, in most patients, both thin and obese, a midline incision carried up along the xiphoid will be adequate. In the obese, extension of the incision below the umbilicus facilitates exposure. Placing the patient in reverse Trendelenburg position is helpful. A nasogastric (NG) tube is placed with its tip at the most dependent portion of the greater curvature. The NG tube helps to keep the position of the esophagus in mind. A self-retaining retractor is required. We use an upper abdominal self-retaining retractor that provides excellent accessories for securing wide exposure to the upper abdomen, and by means of well-placed Mikulicz’s pads, for holding the small bowel and transverse colon in the lower abdomen (Fig. 35-1). Some surgeons advocate routine mobilization of the left lobe of the liver by dividing the left triangular ligament. This mobilization is not always necessary, and when the lobe is floppy, can impede exposure. If this maneuver is performed, the lateral segment of the left lobe is held upward and to the right by a Richardson or Herrington-type retractor accessory. Care must be taken to place sponges or a pack between the retractor attachment and liver, and not to put much tension on the liver to avoid fracture of the liver parenchyma and bleeding.
TRUNCAL VAGOTOMY

Truncal vagotomy (TV) is performed in conjunction with some form of drainage procedure. In the elective setting, it is used in conjunction with antrectomy for definitive management of refractory symptoms of duodenal ulcer, pyloric channel ulcer (gastric ulcer type III), or gastric ulcers combined with duodenal (Dragstedt) ulcers. In the current era of highly effective antisecretory therapies such as omeprazole, and anti-*Helicobacter* antibiotics,
the main indication for TV and antrectomy is in the setting of pyloric outlet obstruction with a longstanding history of ulcer symptoms or complications such as bleeding and perforation. TV and pyloroplasty are reserved for emergency operations for complications such as bleeding or perforation. Occasionally, TV plus gastroenterostomy will be an appropriate compromise when the duodenum is too scarred to permit safe antrectomy and duodenal closure. The anatomy of the vagal trunks and nerves of Latarjet has been reviewed\textsuperscript{17} and is shown schematically in Figures 35-2 and 35-3.

\textbf{FIGURE 35-2} The distribution of the anterior vagus nerve is shown. The \textit{dotted line} indicates the line of dissection. Note that it goes around the incisura to within about 6 cm of the pylorus. The gastrocolic omentum has been partially divided to permit access to the posterior nerve of Latarjet and to allow the stomach to be grasped and used as a retractor. Note that the gastroepiploic arteries are carefully preserved.
FIGURE 35-3 The posterior wall of the stomach and posterior nerve of the Latarjet are shown. The terminal Y fork of the nerve is preserved, and all of the branches to the stomach are divided, leaving about 5 cm of the distal portion of the stomach innervated.

Using a Mikulicz pad or carefully applied Babcock clamps, the assistant places downward traction on the greater curvature of the stomach, thereby placing traction on the gastroesophageal junction and lower esophagus. The first step is to incise the peritoneal covering of the gastroesophageal junction. The peritoneum is opened horizontally, from the angle at the lesser curvature to the cardiac notch at the greater curvature. The surgeon’s thumb and right index finger are used in a blunt dissection to encircle the esophagus. When teaching this maneuver, it is not uncommon for the trainee to confuse the right crus of the diaphragm with the esophagus itself or even the posterior vagal trunk. Extra time spent at this juncture to correctly identify all structures is an essential aspect in teaching the operation. A Penrose drain can be passed around the junction in order to place more effective downward traction on the gastroesophageal junction. When encircling the esophagus, the
surgeon stays wide of the esophagus in order to prevent inadvertent entry into
the lumen and to include the vagal trunks. In the course of this maneuver, the
posterior vagal trunk usually will be palpated as a taut cord.

A single anterior vagal trunk is usually identified in the anterior
midportion of the esophagus, 2 to 4 cm above the gastroesophageal junction
(Fig. 35-4). At this level, however, it is not uncommon for vagal fibers to be
distributed between two or three smaller cords. These cords are palpable as
much as they are visible and can be separated from surrounding esophageal
muscle fibers using a nerve hook. These trunks are individually lifted up, and
2- to 4-cm segments of each are separated from surrounding tissues. A
medium-sized clip is applied at the most superior end, and a clamp is applied
inferiorly. The 2-cm length of nerve is resected and a clip is applied below
the clamp; small bleeders are cauterized precisely. If it has not been done, the
esophagus should be more widely mobilized for a distance of 4 to 5 cm above
the gastroesophageal junction. Smaller, individual vagal fibers that ramify
from the main trunks toward the lesser curvature and the cardiac notch then
can be identified and cut or cauterized. The “criminal nerve” of Grassi,
discussed in more detail in the section describing parietal cell vagotomy, also
may be identified here, wrapping around the cardiac notch from its origin in
the posterior trunk. The posterior vagal trunk itself usually will have been
identified along the right edge of the esophagus. If the anterior vagus has
already been divided, the esophagus is more mobile. This mobility allows the
surgeon to place downward traction on the gastroesophageal junction, or
along the most caudal portion of the greater curvature, thereby applying
gentle tension on the EG junction, which causes the posterior vagus to
“bowstring” and make it easier to identify. A 2- to 4-cm segment is separated
from surrounding tissues, its margins marked with clips, and resected. Major
branches of the anterior vagus and the posterior vagal trunk should be sent to
pathology for examination in frozen section. Care should be taken to note the
results of the pathologist’s frozen section diagnosis in the dictated operative
note.
SELECTIVE VAGOTOMY

Selective vagotomy (SV) is not commonly practiced in the United States, but it has found favor with European surgeons, who prefer not to cut the
posteriorly derived vagal branch that innervates the small intestine and pancreas and anteriorly derived vagal branch that supplies the gallbladder and liver. There is evidence that preservation of such branches can avoid alterations in gallbladder motility that might lead to stasis and stone formation. However, it is not clear whether preservation of the small intestinal and pancreatic nerves protects against some symptoms of the dumping syndrome. SV involves interruption of both nerves of Latarjet and therefore does not avoid the need for a drainage procedure. Thus the main indication for SV may be in patients undergoing elective antrectomy with vagotomy for refractory ulcer symptoms or obstruction.

Exposure to the vagus, gastroesophageal junction, and esophagus is obtained in the same way that the surgeon would perform TV. Anteriorly, the nerve of Latarjet is identified by following the anterior vagal trunk as it descends from the esophagus to the lesser curvature of the stomach. Frequently, the descending branch of the left gastric artery is in close proximity to the site where the hepatic/gallbladder branches take off toward the liver in the gastrohepatic (lesser) omentum. A segment of the nerve of Latarjet is severed between clips and sent for examination on frozen section. The most expeditious way to perform this maneuver is to cross-clamp the portion of the lesser omentum that contains the artery and nerve, ligating and dividing these structures together (Fig. 35-5). The dissection continues upward along the lesser curvature, gastroesophageal junction, and esophagus. Division and ligation of blood vessels and nerves in this bundle avoids the hepatic/gallbladder branches and denervates the cardia, as was described for TV. This dissection opens up the plane for dissection and ligation of the posterior nerve of Latarjet.
**HIGHLY SELECTIVE VAGOTOMY**

Generally accepted indications for highly selective vagotomy (HSV) include elective management of intractable symptoms of duodenal ulcer disease, emergency treatment for perforated duodenal ulcer, and emergency treatment of perforated gastric ulcer when the ulcer is to be excised in a wedge rather than resected in continuity with the distal stomach. HSV also has been advocated for management of bleeding gastric or duodenal ulcers, but this has not been widely practiced. Finally, there is published experience in
pyloric outlet obstruction using HSV in combination with finger or endoscopic balloon dilation,\textsuperscript{19,23–25} but systematic audits of long-term persistence or recurrence rates of obstructing symptoms have yet to be reported.

A number of variations of the technique have been described, and all are not reviewed here. However, it is worth cataloguing the decisions that the surgeon must make in preparing for and performing this operation. In the past, Congo red dye has been utilized for intraoperative testing of the completeness of vagotomy. Currently, it is not approved for use in the United States and is generally unavailable except on protocol. Along these lines, it may be difficult, and sometimes contraindicated, to perform endoscopy in the setting of acute bleeding or perforation. Thus, the use of Congo red is not encouraged except where specific protocols of investigation might require its use.\textsuperscript{26} Conceptually then, the operation is divided into four phases: (1) exposure and gastric mobilization; (2) dissection of the anterior leaf of the lesser omentum; (3) dissection of the posterior leaf of the lesser omentum; and (4) dissection of vagal fibers traveling to the stomach along the distal esophagus.

**Exposure and Gastric Mobilization.** Exposure of the vagus nerves, esophagus, and gastroesophageal junction is obtained as described previously. A wide-bore (18F) NG tube should be placed by the anesthesia team. A number of authors have emphasized the importance of the stomach as a retractor in this operation. We recommend mobilization of the distal part of gastrocolic omentum. The dissection should be carried outside the gastroepiploic arcade, in order to avoid loss of any blood supply to the greater curvature. Congenital adhesions between the stomach and peritoneum overlying the pancreas are divided sharply. The goal of this dissection is to obtain sufficient mobility of the stomach so that it can be rotated upward and to the patient’s right, thus permitting visualization of the posterior leaf of the lesser omentum and the posterior nerve of Latarjet through the lesser sac. The nerve can be seen running close to the descending branch of the left gastric artery. Vagal fibers can be seen running transversely toward the lesser curvature.

**Dissection of the Anterior Leaf of the Lesser Omentum.** The anterior leaf of the lesser omentum now is dissected. The next decision point is to define the distal margin of the dissection of the branches of the nerve of Latarjet (Fig. 35-6). An important landmark is the incisura angularis. The
“crow’s foot” is the neurovascular bundle that innervates the junction of the corpus and antrum, and has three characteristic branches from which its name derives. These nerves contain motor branches to the antrum and secretory branches to the oxyntic mucosa. Thus, leaving this bundle intact makes the antisecretory operation less complete, but fully severing it may lead to disturbances in gastric emptying. Two approaches for defining the distal margin of the dissection have been advocated. First, one may arbitrarily begin the dissection at a predetermined point 6 to 7 cm proximal to the pylorus, a distance that usually corresponds to the most proximal of the three branches of the crow’s foot. Alternatively, one may identify this most proximal branch and begin the dissection there. It is helpful to begin the dissection a few centimeters proximal to the agreed-upon distal margin, because strong traction during subsequent parts of the operation may cause traction injury on the antral motor branches and vessels that accompany them. These last few centimeters are dealt with last.
**FIGURE 35-6** Highly selective vagotomy. **A.** Planned line of dissection of the anterior leaf of the gastrohepatic ligament. **B.** The dissection is carried out, beginning just proximal to the crow’s foot and extending upward, to the left of the gastroesophageal junction.

The assistant provides downward and leftward traction on the greater curvature, thus placing tension on the anterior nerve of Latarjet as it runs along the lesser curvature. The hepatic fibers usually are visualized without difficulty in the upper part of the lesser omentum. It is helpful to “score” the serosa of the lesser curvature, from the incisura to the cardia, and then transversely across the gastroesophageal junction. The incision is performed with dissecting scissors or a no. 15 knife, not electrocautery. This maneuver widens the gap between the nerve and the gastric wall. Individual vessels run transversely from the lesser omentum onto the lesser curvature. These structures are ligated in continuity with 3-0 silk ligatures before division. (We avoid the use of hemostats in this dissection.) This part of the operation is performed gently and should not cause blood loss. The dissection proceeds along the lesser curvature until the gastroesophageal junction is reached. The left anterior aspect of the esophagus is now uncovered, and, for the moment, the dissection stops. Care should be taken not to continue up the right side to avoid interrupting the main anterior vagus.

**Dissection of the Posterior Leaf of the Lesser Omentum.** The posterior leaf of the lesser omentum is then dissected. Care should be taken in setting up exposure for this part of the operation. In one approach, the stomach is rotated upward and to the patient’s right. Alternatively, the posterior leaf can be reached by working through the anterior leaf as illustrated in Figure 35-7. Using the thumbs and fingers, the gastroesophageal junction is “rolled” counterclockwise so that the posterior wall moves to the right and the anterior wall moves to the left. The nerve branches and their accompanying vessels then are ligated in continuity and divided. The dissection should not be carried to less than 6 cm from the pylorus. To avoid the main left gastric vessels, this approach to the dissection should be carried about two-thirds of the distance along the lesser curvature. After reaching the left gastric vessels, the surgeon returns to the anterior approach, ligating and dividing the remainder of the posterior leaf through the window in the anterior leaf.
FIGURE 35-7 Parietal cell vagotomy. **A.** The line of dissection of the posterior leaf of the gastrohepatic ligament is illustrated. **B.** The dissection is carried out through the window created by prior dissection of the anterior leaf.

**Dissection of the Distal Esophagus.** The goal of this dissection is to clear the distal esophagus of all nerve fibers for a distance of approximately 5 cm above the gastroesophageal junction. The importance of this part of the dissection is well documented.\(^{27}\) It should be noted that the prior dissection of the lesser omentum has allowed the main vagal trunks to move upward and to the patient’s right, thereby minimizing the risk of damaging the main trunks in this part of the dissection. The operative technique requires that this dissection stay close to the lesser curvature and esophagus. Any dissection toward the tissues to the right (ie, toward the main vagal trunks) should be avoided.

This part of the procedure begins with the dissection of the left side of the esophagus (Fig. 35-8). Denuding the surface can be performed gently, using a finger or “peanut” dissector to isolate the adventitia that contains nerves, vessels, and lymphatics. This dissection is where the criminal nerve of Grassi is likely to be encountered. Tissues are ligated in continuity and divided. This dissection should also clear 2 or 3 cm of the cardia, just distal to the gastroesophageal junction, and small fibers running to the greater curvature will be divided here. It is usually not necessary to divide any of the short gastric arteries.
FIGURE 35-8 The serosa has been cut to the left of the esophagus, and fatty areolar tissue to the left of the esophagus, containing nerve fibers, blood vessels, and lymphatics, is hooked up by the right index finger. The angle of His and the adjacent esophagus with a 2- to 3-cm portion of the fundus of the stomach are thoroughly cleaned. In this way, small nerve fibers running to the proximal 3-cm portion of fundus (“criminal nerves of Grassi”) are eliminated.

The anterior aspect of the esophagus is now cleared of vagal fibers (Fig. 35-9). Gentle traction and lifting of the fibers will isolate them for division between ligatures or by cautery. We prefer ligation in continuity with fine (4-0 or 5-0) silk to avoid injury to the esophageal muscle. The posterior aspect is now re-exposed with downward traction of the gastroesophageal junction and a counterclockwise rotation of the distal esophagus. Working through the window of the anterior leaflet, the upward branches of the left gastric artery are visualized as they pass to the cardia and the gastroesophageal junction. They are ligated in continuity and divided. The dissection continues upward along the cardia and gastroesophageal junction until it is possible to encircle
the lower esophagus with a Penrose drain. Downward traction on the
gastroesophageal junction is provided by this drain, and additional nerve
fibers are seen in the adventitia. Smaller fibers are cauterized while held
away from the esophageal muscularis, whereas larger ones are ligated with
clips or fine silk and divided. Throughout this dissection, the positions of the
nerves of Latarjet and the main trunks should be checked.

**FIGURE 35-9** Anterior gastric branches of the anterior vagal trunk running
downward on the anterior surface of the esophagus are gently lifted with a
hemostat and either ligated or clipped before being divided or destroyed with
diathermy.

The final part of the operation involves completion of the distal dissection
to the crow’s foot and checks for hemostasis. A number of authors have in
the past suggested that reperitonealization of the lesser curvature be
performed. Although we do not routinely do this, the rationale for this maneuver is that the devascularization that is part of HSV may lead to small areas of necrosis of the gastric wall and localized perforations. Such leaks have been reported in about 0.2% of patients.\(^{28,29}\) Also, it has been argued that reperitonealization might impede reestablishment of vagal nerve connections to the gastric wall.\(^{30}\) The reperitonealization would thus protect against such leaks. The reperitonealization can be performed by inversion of the serosa of the lesser curvature with running or continuous 3-0 long-acting absorbable suture. Alternatively, a vascularized pedicle of omentum can be used to cover the deserosalized lesser curvature. Bleeding complications have been reported with this latter method, but it minimizes tension within the gastric wall.

**REOPERATIVE APPROACHES TO THE VAGUS NERVES**

Approximately two-thirds of patients with duodenal or pyloric channel ulcer recurrence after an initial antisecretory operation (TV, SV, or HSV) have evidence of persistent (or possibly reestablished) vagal innervation.\(^{9,31,32}\) Although many such recurrences are amenable to medical regimens, a small fraction ultimately may be considered for reoperation, especially if surgery is required to control an acute complication such as bleeding or perforation following a period of ulcer-related symptoms. Prior surgery will have made the standard approaches to the lesser curvature and gastroesophageal junction hazardous, which is often caused by dense adhesions to a previously mobilized left lobe of the liver. Thus, two approaches to the vagus, both nonselective, may be considered for completion of the failed vagotomy, especially if it was performed in conjunction with antrectomy. It should be stressed that when such a reoperation is contemplated, especially in a nonemergent setting, it is prudent to obtain some form of acid secretion profile to document the hypersecretory state. Also, because of the nonselective nature of the completion vagotomy, an antrectomy or drainage procedure must be performed.

In the setting in which standard access is difficult due to prior surgery, Barroso and associates have utilized a transabdominal suprahepatic approach to the vagi.\(^{33}\) A high midline incision is used, with mechanical retraction to elevate the subcostal margin. An 18F NG tube is placed. The triangular, left coronary, and falciform ligaments and adhesions are divided, permitting
downward retraction of the left lobe. Using the NG tube, the esophagus and hiatus are located. The esophagus and vagi are dissected at the level of the diaphragm at the hiatus and incised anteriorly for a distance of 3 to 5 cm, exposing the esophagus at the lower mediastinum. The trunks are easily identified and ligated in the untouched lower thoracic esophagus. The hiatus is closed with interrupted nonabsorbable sutures.

A transthoracic approach to this region has also been used, and with the advent of thoracoscopy it may become increasingly attractive for this limited set of patients. Specific issues in anesthesia for this approach have been reviewed. The operation is performed through the left chest, entered via the eighth intercostal space. An NG tube is positioned with its tip in the stomach. After division of the inferior pulmonary ligament, the base of the left lung is retracted upward and laterally. The mediastinal pleura overlying the esophagus is incised for a distance of 8 cm. The esophagus is then mobilized and encircled with a Penrose drain. Vessel loops are used to retract individual vagal trunks as they are identified. The supradiaphragmatic anterior vagus nerve may have multiple branches above the level of the diaphragm, but rarely are there multiple branches at a level 4 cm above the diaphragm. In contrast, the posterior vagus has multiple branches above the level of the diaphragm but is a single trunk at this level more than 90% of the time (Fig. 35-10). Thus, the best opportunity for a complete vagotomy lies 4 cm above the diaphragm for the posterior trunk. A circumferential dissection of the 6 cm of esophagus just above the diaphragm is carried out, with technique similar to that performed during the HSV. Tube thoracostomy is required for 2 to 3 days postoperatively.
FIGURE 35-10  Anatomy of the anterior (A) and posterior (B) vagus nerves above the diaphragm in 50 cadavers. Incidence of each anatomic group is indicated by percentage. (Reproduced with permission from Jackson RG: Anatomy of the vagus nerve in the region of the lower esophagus and stomach, *Anat Rec* 1949;Jan;103(1):1-18.)

**DRAINAGE PROCEDURES**

In the context of bilateral truncal or selective vagotomies, the purpose of a drainage procedure is to preserve the pylorus but bypass it or render it ineffective. The options for drainage include (1) gastroenterostomy; (2) pyloric dilation; (3) pyloromyotomy; and (4) pyloroplasty. Generally, these techniques are used when TV or SV is performed, but they also may be used with HSV in order to treat obstruction resulting from peptic acid scarring. We discuss techniques for performing gastrojejunostomy in the subsequent discussion of gastric resection.
Pyloric Dilation

In open procedures, the simplest technique reported for performing pyloric dilation is to perform a small gastrotomy, approximately 3 to 4 cm in length, proximal to the pylorus. A finger is introduced through the pylorus, forcing it to widen. The gastrotomy then is used with a single layer of 3-0 silk interrupted sutures or staples. A second technique, advocated for use in laparoscopic cases, is to use a balloon. The balloon, 15 mm in length, may be positioned through a gastrotomy, endoscopically, or with radiologic control, and inflated to 45 psi (pounds per square inch) for 10 minutes. Other dilators are available for positioning over a wire and inflation to higher pressures, which may prevent pyloric spasm. Advocates of pyloric dilation after laparoscopic TV or SV have suggested that a drainage procedure is not required as often as previously thought or may only be necessary in the early postoperative phase and not permanently. Thus, it is argued that dilation can be repeated postoperatively and in the outpatient setting. Most surgeons, however, subscribe to the need for some form of formal drainage procedure after SV or TV.

Pyloromyotomy

Pyloromyotomy is performed using the same techniques as those described in the setting of hypertrophic pyloric stenosis in the infant (Fig. 35-11). An incision is made to score the anterior surface of the stomach from 1 to 2 cm proximal to 1 cm distal to the pyloric ring. The separation of pyloric muscles is accomplished mainly with a fine-tip hemostat and the knife. Cautery is avoided and only used in the muscularis, not the submucosa. When this procedure is performed in the setting of esophagogastrectomy, the pylorus is usually soft and unscarred. In the setting of chronic duodenal ulcer disease, the pylorus is often scarred, and it is difficult to perform the gentle, meticulous dissection of muscle layers, which is required, and at the same time to avoid entering the mucosa. Laparoscopic versions of this procedure also have been advocated in the setting of laparoscopic TV or SV. Occasionally omentum is placed over the myotomy.
**FIGURE 35-11** Pyloromyotomy. **A.** Dissection of seromuscular layers, avoiding entry into bowel. **B.** An omental patch is used to cover the dissected area.

**Pyloroplasty**

The most expeditiously performed pyloroplasty is the Heineke–Mikulicz procedure ([Fig. 35-12](#)). This is difficult to perform if the pyloric region is very scarred. The operation usually is performed in the setting of emergency surgery for bleeding or perforation of a gastric or duodenal ulcer. A vagotomy is performed, usually after bleeding has been controlled. If the indication is a bleeding or perforated duodenal or pyloric channel ulcer, the incision for pyloroplasty may include the ulcer or be used to gain access to the ulcer. The incision is thus the planned pyloroplasty incision.
FIGURE 35-12 Heinecke−Mikulicz pyloroplasty. A. Full-thickness incision extends from 2 cm proximal to 1–2 cm distal to the pyloric ring. B. The incision is closed vertically. C. Illustration of Gambee stitch. D. Finished pyloroplasty.

It is not always necessary to perform a Kocher maneuver; however, duodenal mobilization is usually helpful in relieving any tension on the intended suture line. Unless the duodenal bulb is unusually mobile, we recommend this as the initial step. In this maneuver, the peritoneum along the right border of the duodenum is incised from the lateral border of the common bile duct to the junction of the second and third portions of the duodenum. After duodenal mobilization, 3-0 silk stay sutures are placed untied, superior and inferior to the site of the intended incision, which then is made on the anterior surface in a longitudinal direction, using electrocautery, from 2 cm distal to the pyloric muscle to 3 cm proximal to the pylorus. The closure of the pyloroplasty is performed vertically, in order to minimize narrowing of the lumen. The Gambee stitch (see Fig. 35-12) is a single-layer inverting suture used in this setting. The suture, usually performed with 3-0 or 2-0 silk, begins on the outside and is (1) placed full thickness (serosa to mucosa) on the same side; (2) brought, on the same side, back through the mucosa to the submucosa; (3) carried through the submucosa to the mucosa on the opposite side; and (4) brought full thickness from mucosa to serosa on that side. When the pylorus is scarred and the tissues inflexible, it is often helpful to tie the sutures after they have been placed rather than as they are being placed. The stay sutures then are removed after completion of the pyloroplasty. A tongue of vascularized omentum (as shown for pyloromyotomy in Fig. 35-11) may be brought up to cover the closure and is sutured to the gut wall with 3-0 absorbable (polyglactin 910) sutures.

The Finney pyloroplasty can be used when scarring has involved the pylorus and duodenal bulb and would not permit a tension-free, patulous Heineke−Mikulicz pyloroplasty. The Finney pyloroplasty is in essence a side-to-side gastroduodenostomy (Fig. 35-13). When this operation begins, dense adhesions often are encountered surrounding the pylorus and duodenal bulb. These must be lysed systematically. The Kocher maneuver then is performed, carrying the mobilization distally. Complete mobility of the duodenum and freedom from surrounding adhesions are essential to this operation.
FIGURE 35-13 Finney U-shaped pyloroplasty. A. The distal stomach and proximal duodenum are aligned with traction strands and their adjacent walls approximated with a Cushing suture; the inverted U-shaped incision into the lumens of the stomach and duodenum is indicated. B. Suture of the posterior septum of the stomach and duodenum. C. The first anterior tier of sutures
(Connell) is placed. The operation is completed with a reinforcing tier of Cushing sutures.

A 2-0 silk stay suture is placed on the upper anterior surface of the pyloric ring. Another stay suture is placed on the greater curvature of the stomach approximately 10 cm proximal to the pylorus, and a third stay suture is placed approximately 10 cm distal to the pylorus. Traction cranially on the pyloric suture and caudally on the other two sutures brings the anterior surfaces on the stomach and duodenum into apposition. The apposed surfaces are sutured together using interrupted 3-0 silk Lembert seromuscular sutures. Using electrocautery, an inverted U-shaped incision is made beginning on the gastric side just distal to the traction suture, traveling longitudinally through the pylorus, then distally to a point just proximal to the traction suture. If the ulcer is present on the anterior surface of the duodenal bulb, it is excised. The posterior inner layer between the stomach and the duodenum then is sutured closed with a continuous over-and-over 3-0 Vicryl, chromic catgut suture, or DDS. This closure is begun at the superior edge, carried caudally, and then converted into a Connell inverting technique as the suture is brought around the inferior edge to begin closing the anterior portion of the inner layer. The anterior outer layer then is closed using interrupted 3-0 seromuscular inverting sutures (Lembert) sutures. Some surgeons use 3-0 Maxon or PDS suture material for single-layer continuous closure, as additional insurance against a suture line leak.

GASTRIC RESECTIONS

The common indications for gastric resections include peptic ulcer disease and tumors of the stomach. Safe performance of gastric resection requires an understanding of the following: (1) the physiology of vagal innervation and gastric emptying; (2) the surface and vascular anatomy of the stomach; (3) the principles of reconstruction following resection, specifically the Billroth I (B-I) gastro-duodenostomy, the Billroth II (B-II) gastro-jejunostomy, and the Roux-en-Y configuration; (4) the principles of surgical stapling techniques as well as hand-sewn suturing techniques; and (5) the specific early and late postoperative complications that arise from different gastric resections and different forms of reconstruction. Degrees of resection are correlated to the surface anatomy, as shown in Figure 35-14. This discussion is divided into
three sections. The first section describes techniques for performing wedge resections and closure of gastric wall for ulcers, polyps, or tumors derived from neuroendocrine elements or stromal tissue. Carcinomas are not amenable to wedge resection, and curative resection should involve formal regional gastrectomy and lymphadenectomy. Palliative resection, however, for bleeding or obstruction, may involve either a wedge resection or formal resection. The second section describes techniques for distal gastric resection, focusing on antrectomy or hemigastrectomy (with or without vagotomy) for peptic ulcer disease and when the major decision involves the choice of B-I or B-II reconstruction. The third section describes techniques used in management of gastric carcinoma, focusing on proximal, subtotal, or total resection, and the techniques of regional node dissection.

![Diagram of stomach resections]

**FIGURE 35-14** Amount of stomach removed in antrectomy or hemigastrectomy: 60% to 75% for partial gastrectomy and 80% or over for subtotal gastrectomy. Note that most of the lesser curvature of the stomach is excised in all these resections.

**Wedge Resection of the Stomach**

Exposure is gained through an upper midline incision, carried from the xiphoid to the umbilicus. A Bookwalter or other self-retaining mechanical retractor is highly desirable, especially for lesions located on the lesser
curvature or the proximal stomach. The technique of wedge resection depends on the location of the lesion. When a gastric tumor, such as a carcinoid or gastrointestinal stromal tumor (GIST), is located on the greater curvature of the stomach, it is important to note the proximity to the pylorus or gastroesophageal junction. Wedge resection may not be possible if the lesion lies too close (within 2 cm) to these borders, because the closure might narrow the lumen and cause partial obstruction to the flow of chyme. Formal resection may then be necessary. If proximity to these borders is not a problem, omental adhesions to the tumor are left in contact with the lesion. Farther away from the tumor, the portion of the omentum that is adherent is divided between clamps and will come with the specimen. Branches of the gastroepiploic arteries that supply the gastric wall adjacent to the tumor are ligated in continuity with 3-0 silk ligatures and divided. The gastroepiploic artery need not be divided unless it is adherent to the surface of the tumor. At a distance of 2 cm from the base of the tumor, the serosa of the gastric wall is scored using cautery, inscribing a circle. The cautery is then used to deepen the incision through the muscularis. As the muscularis is divided, submucosal bleeders will pop through, requiring precise cauterization to secure hemostasis. When the tumor and the surrounding gastric wall have been excised, the gastrotomy is closed longitudinally in two layers. The inner layer is a full-thickness hemostatic layer sewn continuously using 3-0 chromic or Vicryl suture and the outer layer used interrupted seromuscular 3-0 silk Lembert sutures. An omental patch is not necessary unless there are specific concerns about the blood supply to the closure. When situated favorably, such lesions are also amenable to laparoscopic resection\textsuperscript{41–43} and to combined endoscopic-laparoscopic approaches involving intraluminal resections.\textsuperscript{44,45} As long as the lumen is not compromised, stapled or open excision is possible.

When tumors are located on the lesser curvature or it is necessary to perform a gastrotomy in order to stop ongoing bleeding from a gastric ulcer, the excision can be performed from the mucosal side of the lesion (Fig. 35-15). Once the inside borders of the lesion have been identified, it is important to obtain optimal exposure of the lesion from the serosal aspect. It may be necessary to sacrifice one or both nerves of Latarjet or the left or right gastric arteries, and this determination can only be made from the outside of the stomach. A stapled option also exists if the lesion can be excised without narrowing the lumen. If the lesion is located on the lesser curvature and
cannot be removed without sacrifice of both nerves of Latarjet, a pyloroplasty should be performed. In such cases, our preference is that the resection is extended to include the distal stomach and a B-I or B-II reconstruction (Fig. 35-16). One variation on this latter approach for high-lying bleeding or perforated gastric ulcers is Pauchet’s operation, a modification of an operation described by Shoemaker. This procedure involves removal of the antrum and a tongue of the corpus that extends upward to include the ulcer (Fig. 35-16E).46
FIGURE 35-15 Small tumors or polyps not amenable to endoscopic polypectomy can be excised with surrounding wedge of normal gastric wall. A. A 2-cm margin is advisable. B. The gastrotomy can be closed in one or two layers, using 2-0 nonabsorbable sutures sewn in interrupted fashion.


Distal Gastric Resections and Reconstruction

VAGOTOMY AND ANTRECTOMY

An antrectomy for duodenal or pyloric channel ulcer removes about 35% of the distal stomach and must include the entire non–acid-secreting portion. The incision is made in the upper midline and a Bookwalter or other self-retaining mechanical retractor is helpful. An NG tube is positioned under the
The distal stomach is mobilized in the following fashion: first, the lesser sac is entered by incising the gastrocolic ligament. These attachments are sometimes avascular but usually are divided between clamps and ligated with 3-0 silk ligatures. The stomach may thus be lifted upward, revealing the posterior gastric wall. Congenital adhesions from the posterior wall and pancreas capsule are divided sharply. The dissection is carried distally along the greater curvature (Fig. 35-17), dividing the small branches of the gastroepiploic artery to the gastric wall. The dissection reaches the main right gastroepiploic artery, which sometimes has to be divided between Kelly clamps and ligated with 2-0 silk ligatures. When possible, the dissection should be carried between the gastric wall and artery, thereby preserving the main gastroepiploic artery as additional collateral blood supply to the suture lines and coming anastomosis. When the dissection reaches the pylorus, small bleeders should be divided between fine hemostats and ligated with fine silk ligatures. The dissection should be meticulous and gentle, because pancreatic tissue lurks in this area and inflammation can be activated in this dissection. The dissection should be carried about 1 cm past the pylorus if a B-I reconstruction is anticipated. If B-II is anticipated, the dissection need only be carried far enough to comfortably place the transverse linear stapler past the pylorus or to oversew the duodenum by a hand-sewn technique.
FIGURE 35-17  Billroth I operation. A. Use of the ligate-divide-stapler, LDS II. This instrument, employing a disposable cassette, applies two stainless steel clips and cuts between, thus reducing operating time and effort significantly. B. Extent of dissection of lesser curvature. C. Division of vessels entering the lesser curvature in much the same way as when performing proximal gastric vagotomy.

The assistant’s left hand is used to lift the distal stomach forward and inferiorly. The more flimsy tissues of the lesser omentum are divided along the lesser curvature, using electrocautery. Starting at the incisura and working toward the pylorus, the tissues of substance are divided between clamps and ligated with 3-0 silk ligatures. This dissection generally will include the
descending branch of the left gastric artery. When the right gastric artery is reached, it is divided and ligated with 2-0 silk ligatures. At this point (Fig. 35-18), we prefer to divide the stomach. This is accomplished with a 90-mm GIA stapler or the gastric TA-90. If the latter stapler is used, the stomach distal to the staple line is occluded with a crushing intestinal clamp and the gastric wall is divided. The clamp is then used as a handle for manipulating the distal stomach. The final portion of the dissection involves gentle dissection of the posterior duodenal wall from the pancreas. Because this dissection may involve separation of pancreas elements from the posterior duodenal wall, cautery is used minimally or not at all and tissues are separated gently with fine hemostats and ligated with 4-0 silk. If a B-I anastomosis is anticipated, the duodenum is divided using the electrocautery, just distal to the pyloric ring. If a B-II anastomosis is anticipated, the transverse TA-30 stapler is placed flush with the pyloric ring. After firing the stapler, a knife is used to sever the pylorus from the staple line. The specimen then is removed to a sterile table. The staple line can be inverted with 3-0 silk Lambert sutures or covered with an omental patch if there is a concern about vascular supply or tension in the staple line. The specimen can then be opened and turned inside out to reveal the gastric mucosa. The proximal border of the resection should contain transverse and obliquely oriented rugae characteristic of the acid-secreting gastric corpus and distinguishable from the longitudinally oriented antral folds. This maneuver verifies complete removal of the antrum.
Billroth I reconstruction. When distal gastrectomy is performed for type I gastric ulcer, B-I anastomosis is preferable. A B-I anastomosis can be used safely for duodenal or pyloric channel ulcer if scarring of the duodenal bulb and pylorus are minimal. If this form of reconstruction is planned, a Kocher maneuver should be performed prior to distal gastrectomy. This will help to minimize tension on the anastomosis. As shown in Figure 35-19, the lower portion of the gastric staple line is removed by excision of gastric wall just posterior to the staple line. The length of the staple line to be removed is the width of the duodenal stump. The gastroduodenostomy is performed in two layers (Fig. 35-20). The posterior layer of interrupted 3-0 silk Lembert
seromuscular sutures is placed first. The inner 3-0 Vicryl sutures are placed next to each other, sewn away from each other in an over-and-over fashion until the sutures are brought around the edges to the anterior aspect. Connell sutures are used to invert the inner anterior layer. The anterior outer layer is closed with interrupted 3-0 silk Lambert sutures. The junction of the sewn anastomosis and superior portion of the gastric staple line has been called the “angle of sorrow” because of the complication of leakage where these suture/staple lines meet. A number of authors recommend inversion of the upper staple line by 3-0 silk Lembert sutures and a special covering suture for this junction. A second strategy is to cover this area with a tongue of omentum.

**FIGURE 35-19**  Billroth I operation. Division of the lower portion of the suture line.  
**A.** The line of transection from the greater curve to the mid portion of the staple line.  
**B.** With the stomach clamped a scalpel blade is used to incise the stomach.  
**C.** Completion of the transection where the anastomosis will be performed.
FIGURE 35-20 Billroth I operation. The construction of the gastroduodenostomy is performed end to end in two layers. **A.** The posterior row of interrupted sutures. **B.** The posterior row of the inner layer using a running suture. **C.** The completed anastomosis.

A B-I anastomosis also may be performed using mechanical stapling techniques. As shown in Figure 35-21, the duodenum is transected just distal to the pylorus with the knife and a purse-string suture is positioned circumferentially around its edge. The anvil of the circular stapler, usually a size 25 mm, is secured in the duodenal stump by the purse string. The circular stapler is inserted through an anterior gastrotomy and fired through the posterior wall of the stomach (Fig. 35-22). It is important that the margin of the stapled suture line be placed 3 cm proximal to the stapled gastric closure, to provide maximum blood supply to both staple lines. The anterior gastrotomy then is closed with a TA-55 stapler or sutured closed in two layers.
A. A Dennis clamp can be placed across the proximal duodenum, and the purse-string device can be placed at the selected site of duodenal division. B. A gastrotomy is made with the cautery on the anterior surface of the stomach, carefully avoiding large vascular arcades. This should be done at least 3 cm proximal to the row of staples. The gastrotomy should be large enough to accommodate the end-to-end stapling device easily.
Arm of stapler penetrating posterior stomach 2–3 cm from stapled transection

Securing duodenum over anvil of stapler

Completed gastrojejunostomy

Trimming excess tissue from stapled gastrostomy
FIGURE 35-22  A. The gastrotomy edges should be grasped with two Babcock clamps, and the end-to-end stapling device, minus the anvil, should be passed into the lumen of the stomach. The center rod should be gently pressed against the posterior wall of the stomach approximately 4 cm from the gastric line, and cautery should be used to permit passage of the rod through the posterior wall of the stomach. A purse-string suture will ensure that the stomach does not tear at the site of center rod penetration. The selected anvil size should be applied, and the open end of the duodenum should be grasped with Allis clamps. The duodenal wall should be gently pulled over the anvil, and the purse-string suture should be snugly tied around the center rod. B. The cartridge and the anvil should then be approximated, being certain that no extraneous tissues are caught between the anvil and the circular cartridge. The instrument should be fired, and the anastomosis should then be carefully observed by direct visualization to ensure that hemostasis is adequate. The surgeon should then remove the anvil and check the circular tissue from both the duodenum and the stomach to be certain that the tissue doughnuts are intact. If the doughnuts are defective, external Lambert sutures will need to be applied to secure a complete anastomosis. The gastrotomy is closed by grasping each end with Allis clamps and incorporating the entire thickness of the stomach wall through the jaws of the 55-mm stapler.

Billroth-II Reconstruction. When scarring or undue tension precludes B-I anastomosis following distal gastrectomy, a B-II gastrojejunostomy is indicated. Before describing our technique, it is worth pointing out the decisions that one will make in performing this reconstruction.

Closure of the Duodenal Stump. The first set of decisions focuses on the technique used for closure of the duodenal stump. Careful attention should be given to mobilizing the duodenal stump and obtaining a secure tension-free closure. If the duodenum is relatively free of scar or inflammation, this presents no problem and the TA-55 or TA-60 stapler may be used for closure as described previously. If heavily scarred, dissection of the duodenum and performance of the antrectomy may be abandoned in favor of a safer vagotomy and gastroenterostomy.

If one is committed to the antrectomy and scarring prevents mobilization of the pylorus and duodenal bulb, one may rarely find a need to perform a Bancroft procedure, in which the most distal portion of the pyloric channel and antrum are left in situ after resection of the more proximal antrum (Fig.
The mucosa of the retained segment is stripped, removing all gastrin-secreting tissue that could cause a retained antrum syndrome. In the classic approach for this procedure, the greater and lesser curvatures are mobilized without dissecting too far into the tissues surrounding the pylorus. About 7 to 8 cm from the pylorus, the seromuscular coat of the antrum is incised circumferentially down to the level of the submucosa. Using sharp dissection, the muscle coat is separated from underlying mucosa. This dissection can be facilitated by submucosal injection of 1:100,000 epinephrine solution, as has been described for the mucosal proctectomy in ileal pouch–anal anastomosis procedures. When the pyloric channel opening is reached, a fine purse-string absorbable suture (3-0 chromic catgut or Vicryl) picks up small bites of submucosa at the pyloric ring. Transfixion and ligation of the mucosa is tempting, but it should be avoided as this would lead to mucosal ischemia and subsequent perforation. A small margin of mucosa is left to be invaginated into the pylorus as the purse string is gently closed and tied. The proximal margins of the seromuscular cuff are excised, leaving just enough to close over the purse string. Omentum is used to cover this closure, if possible.
FIGURE 35-23 Bancroft procedure. A. Dissection of the mucosal from the pylorus and antral muscular layers. B. The site of mucosal transection and preservation of the pyloric musculature. C. Oversewing of the duodenal stump.

One other important circumstance to be prepared for is the closure of the duodenum distal to a posteriorly perforated or deeply penetrating ulcer. In this setting, the ulcer crater is left in situ (Fig. 35-24). In other settings, the anterior wall of the duodenum can be sutured to the ulcer base, with care being taken to suture-ligate any exposed vessels. The suture line can be protected by a vascularized tongue of omentum.
FIGURE 35-24 Closure of a chronic, ulcer-scarred duodenal stump. A. The ulcer crater is opened and the duodenum sutured closed. B. The anterior edge of the ulcer crater is used to oversew the duodenal closure. C. A tongue of omentum is tied down to this layer of suture.

**Position of the Jejunal Loop: Antecolic or Retrocolic.** The second decision in performing a B-II reconstruction is whether to bring the loop of jejunum behind (retro) or in front of (ante) the transverse colon. In performing the gastrectomy for benign disease, there is no clear evidence that this makes any difference, and we prefer the retrocolic position. For malignant disease, it has generally been held that the retrocolic position may be predisposed to obstruction owing to enlargement of lymph nodes or serosal implants in the transverse mesocolon. Whether or not this predisposition exists, positioning the jejunal limb in front of the colon requires a somewhat longer mesentery. As long as the anastomosis will not be under tension, the antecolic position will permit emptying as effective as that through a retrocolic anastomosis. If a retrocolic position is chosen, the window in the transverse mesocolon should be wide enough to permit both the afferent and efferent limbs of the jejunum to slide comfortably through. When this window is closed following construction of the anastomosis, it is preferable to tack the mesentery above, on the gastric side, rather than on the jejunal side. This will prevent kinking and obstruction of the jejunal limbs and positions the anastomosis below the mesentery.

**Length of the Afferent Limb.** The third decision is the choice of the segment of jejunum used for the anastomosis. In general, the segment should be as close to the ligament of Treitz as possible and still reach the stomach without tension. This generally leaves 10 to 20 cm of the proximal jejunum as the afferent limb. The shorter this length, the less likely the possibility of an afferent limb syndrome developing. The incidence of other complications such as alkaline reflux gastritis, dumping, or postvagotomy diarrhea should not be influenced by the length of the afferent limb.

**Anastomosis: Site on the Gastric Wall and Technique.** Schematically illustrated in Figure 35-25 are a number of described variations on the B-II reconstruction. We describe here one hand-sewn and one stapled technique for anastomosis. As shown in Figure 35-26, a portion of the gastric staple line is excised with electrocautery, taking a small wedge of stomach behind the staple line. The superior portion of the staple line can be reinforced with 3-0
silk Lembert sutures at this time or can be reinforced later by tacking the afferent limb of jejunum, just beyond the anastomosis, to the gastric wall. The proximal jejunal limb is brought, untwisted, through a window in the transverse mesocolon (Fig. 35-27). Traction seromuscular sutures (2-0 or 3-0 silk) are placed at both corners of the anastomosis. The gastrojejunal anastomosis is performed in two layers (Fig. 35-28), between the most caudal part of the stomach and the jejunal limb. The outer layer is composed of 3-0 silk Lembert seromuscular sutures. The inner layer is performed in the posterior row by running two 3-0 Vicryl sutures in opposite directions around the corners and then in Connell fashion for the anterior row. Placement of the anastomosis on the posterior gastric wall, about 2 to 3 cm from the gastric staple line, also will provide a suitably dependent position for drainage of gastric contents. The window in the transverse mesocolon is closed, as illustrated in Figure 35-29.
FIGURE 35-25  Billroth II operation and some of its modifications.

FIGURE 35-26  Billroth II operation. The antrum is resected as in a Billroth I operation. The distal portion of the resection line is excised. A. The line of transection from the greater curve to the mid portion of the staple line. B. With the stomach clamped a scalpel blade is used to incise the stomach. C. Completion of the transection where the anastomosis will be performed.
FIGURE 35-27  Billroth II operation. The jejunal segment, located 10 to 20 cm beyond the ligament of Treitz, is brought through a window in the retrocolic mesentery.

FIGURE 35-28  Billroth II operation. The gastrojejunal anastomosis is constructed in two layers, as described in the text.
FIGURE 35-29  Billroth II operation. The retrocolic window in the mesentery is closed in order to avoid herniation of other viscera. The mesentery is linked to gastric wall, positioning the anastomosis below the closure.

Illustrated in Figures 35-30 and 35-31 is the technique for stapled gastroenterostomy. As before, the jejunal limb is placed in the retrocolic position. Traction sutures are placed on the gastric wall posterior to the anastomosis, bringing the jejunal limb into apposition. The 55-mm GIA stapler is fired after its two limbs are placed through a small gastrotomy and small enterotomy, respectively. The open end of the anastomosis is then closed with a TA-55 stapler. It should be noted that these staple lines, especially from the TA-55, are difficult to reinforce without undue tension. The blood supply of the gastric and intestinal walls is ample, and reinforcement with Lembert sutures generally is not necessary.
FIGURE 35-30 Stapling technique for Billroth II gastrojejunostomy. A. A gastrotomy and enterotomy are made to accommodate the stapler. B. The stapler is positioned to create the anastomosis.
FIGURE 35-31 A. Billroth II operation. B. and C. The transverse stapler is used to close the common opening over the gastrojejunal anastomosis.

Subtotal and Total Gastric Resections

The main indications for subtotal (70%-80%) gastric resection are carcinoma of the antrum or pylorus or primary gastric lymphoma, although resection for lymphoma is quite rare given the increasing success of medical therapy. However, in cases of ulcers that lie very proximal on the lesser curvature, the proximity to the gastroesophageal junction prevents excision without significant narrowing of the gastric inlet. Similarly, the main indication for
total gastric resection is a bulky carcinoma of the body or distal fundus or a carcinoma of the proximal stomach, and rarely, otherwise unmanageable symptoms of an unresectable gastrinoma. Indications for near-total (>90%) gastric resection include the uncommon settings of the Roux stasis syndrome and gastroparesis unresponsive to medical management, as well as carcinoma or lymphoma of the body of the stomach. The approaches for subtotal and near-total gastrectomy are discussed here only briefly, focusing on issues of exposure and techniques for resection of the stomach itself and reconstruction. The principles of resection for gastric carcinoma will be presented subsequently in conjunction with the discussion of radical total gastrectomy for carcinoma.

**SUBTOTAL AND NEAR-TOTAL GASTRIC RESECTIONS**

In principle, a subtotal gastrectomy is simply an extended antrectomy or hemigastrectomy. A few technical issues are worth noting. First, the exposure provided by a midline incision is usually adequate, although some surgeons may prefer a chevron incision. Second, the left gastric artery always is ligated and divided in this dissection, and once the level of gastric transection has been determined, the branches of the left gastroepiploic artery and short gastric arteries are ligated in continuity and divided up to this predetermined level. Third, in opting for a near-total gastric resection, a 1- to 2-cm cuff of gastric wall is left behind and is the margin for the anastomosis. For this operation, it is desirable to preserve the uppermost one or two short gastric vessels in order to ensure the adequacy of the blood supply for the gastric side of the anastomosis.

One final issue is that a greater extent of lymph node dissection has shown improvement in survival for gastric cancer after resection, although with increased morbidity in some but not necessarily in all centers. Extended lymphadenectomy (D2 resection) involves dissection and removal of the perigastric lymph nodes as well as those of the named vessels of the celiac axis, and the hepatoduodenal ligament. Skeletonization of the celiac artery and its branches (left gastric artery, common hepatic artery, and splenic artery) is required to achieve adequate lymphadenectomy. While performance of a D1 versus D2 lymphadenectomy had previously been debated, modified D2 lymphadenectomy (which excludes distal pancreatectomy or splenectomy for retrieval of lymph nodes) has now become standard of care in resections...
for carcinoma and has been shown to contribute to improved survival.\textsuperscript{55,56} Finally, although it is often possible to reconstruct with a standard gastrojejunostomy, we prefer a Roux-en-Y reconstruction because this minimizes tension on the suture line, incidence and symptoms of bile reflux, and theoretically reduces the risk of anastomotic obstruction by persistence or recurrence of tumor.

**TOTAL GASTRECTOMY FOR CARCINOMA**

The goals of total gastrectomy for carcinoma are (1) clearing of margins on both esophageal and duodenal sides; (2) removal of local and regional lymph node–bearing tissues, including those surrounding the right and left gastric arteries, celiac axis, and named branches of the celiac axis, right gastroepiploic artery, and short gastric arteries; (3) removal of the omentum en bloc with the stomach; and (4) removal of the lymphatic tissues overlying the pancreatic capsule. Extended lymph node dissection (modified D2 resection) should be done here as described in earlier.\textsuperscript{40–43} After total gastric resection, we favor a Roux-en-Y reconstruction with a direct esophagoenterostomy rather than a jejunal pouch, although the techniques for both forms of reconstruction will be described.

Illustrated in Figure 35-32 is the final specimen in an en bloc resection. Generally, an upper midline or chevron incision will provide good exposure. A thoracoabdominal incision (Fig. 35-33) is rarely necessary but can provide better exposure when the patient’s habitus suggests a deep hiatus. This latter incision also should be considered when preoperative endoscopy suggests that the tumor is close enough to the cardia so that the distal thoracic portion of the esophagus might be included with the resection. If this latter approach is chosen, the abdominal portion of the incision is performed first, in order to assess resectability. The patient is placed in a left thoracotomy position. The incision is carried from the line of the eighth rib obliquely toward the umbilicus. If resection appears feasible, the incision is extended over the eighth rib to the posterior angle. Occasionally, the seventh rib will provide better exposure. A separate rib retractor for the chest and a self-retaining retractor without a ring for the abdominal portion provide the best retraction. The diaphragm is divided toward the hiatus, but the muscle does not always have to be divided completely. Thus, it may be possible to spare the neurovascular bundle. Significant bleeding is encountered and this requires
suture ligation with 2-0 or 0-0 Vicryl.

FIGURE 35-32 Anatomy relevant to resections for gastric carcinoma.
Thoracoabdominal incision for radical total gastrectomy for carcinoma of the stomach. The incision is carried along the seventh or the eighth interspace.

In the abdominal approach, the Bookwalter retractor is used. A thorough examination of the entire abdomen must be undertaken to exclude subradiologic metastatic disease. Extra care in positioning retractors on the left lobe of the liver, diaphragm, and small intestine for optimal exposure of the hiatus is time well spent. The dissection is begun by dividing the omentum from the transverse colon (Fig. 35-34). This relatively avascular plane can be separated using the electrocautery. Deviation from this plane will injure the colon or require tedious ligation and division of omental or mesenteric blood vessels. The lesser sac is then entered, allowing assessment of the retroperitoneum with regard to local tumor extension and lymph node
involvement. The distal portion of the gastrectomy is then performed. The origin of the right gastric artery at the common hepatic artery is identified, ligated in continuity with 2-0 silk ligatures, and divided.

FIGURE 35-34 Resection for gastric carcinoma. The gastrocolic omentum is detached from the transverse colon using electrocautery.

Lymphatic-bearing tissues are swept toward the gastric side. The right gastroepiploic artery is identified, usually by palpation, and traced as far to its base as possible. It is usually possible to trace the artery to its origin at the gastroduodenal artery, which is similarly ligated in continuity and divided. Using the electrocautery, the gastrohepatic ligament is incised near the liver and its tissues are swept toward the lesser curvature, from the duodenum to the esophagus. Any small vessels are ligated with 3-0 ligatures. The dissection is carried onto the peritoneal surface of the esophagus. The duodenum may then be divided using the GIA stapler or a TA-55 stapler that is fired twice, once on the duodenum and once directly on the pylorus. The
duodenum is divided just distal to the pyloric ring (Fig. 35-35).

**FIGURE 35-35** Resection for gastric carcinoma. The duodenum is divided beyond the pylorus. Either the linear cutter or transverse stapling instruments are appropriate. If feasible, the duodenal staple line is reinforced using 3-0 silk Lambert sutures.

With the distal portion of the stomach divided, full access to the left gastric artery is obtained posteriorly through the lesser sac. This approach optimizes visualization of the celiac axis and its branches. With the assistant retracting the stomach upward and anteriorly, a number of congenital adhesions between the posterior gastric wall and the peritoneum overlying the pancreas are observed (Fig. 35-36). If tumor is invading this plane, a
decision must be made regarding inclusion of the body and tail of the pancreas in the specimen. The plane made by the peritoneum overlying the pancreas is a natural plane, and there may be sense in taking this peritoneum with the en bloc specimen. This layer can be dissected off the anterior face of the pancreas and swept gently to the front toward the left gastric vessels and splenic hilum. If a curative resection appears to be feasible but would require removal of the body and/or tail of the pancreas, this is not a contraindication to resection. The origin of the left gastric artery is then identified at the celiac axis, ligated in continuity using 2-0 silk, and divided (Fig. 35-37). The stump of the artery is suture-ligated as well. From the celiac axis side, the tissue surrounding the artery contains lymphatics and is swept toward the lesser curvature. Lymphatic bearing tissues overlying the individual celiac axis branches, including the common hepatic artery, left gastric artery, and splenic artery, must be included within the specimen. When the tumor is located in the more proximal body and corpus, the case for inclusion of the spleen with the en bloc specimen has not been persuasive; a recent meta-analysis suggested no oncologic benefit for removal of a spleen not apparently involved by direct extension. Inclusion of the spleen is indicated if there are obvious tumor-bearing nodes or if there is direct invasion of the splenic hilum. Through the lesser sac, the tail of the pancreas is identified. The splenic artery and vein are separated, suture-ligated, and divided individually. At this point, the short gastric vessels are then part of the en bloc specimen and are not dissected or divided.
FIGURE 35-36 Resection for gastric carcinoma. With the lesser sac fully visualized, the thin layer of tissue overlying the pancreas is exposed and can be removed with the en bloc specimen.
FIGURE 35-37 Resection for gastric carcinoma. Exposure of the left gastric artery through the lesser sac.

The posterior aspect of the esophagus then comes into view as the stomach and spleen are lifted upward. Posteriorly, the front of peritoneal tissue can be dissected bluntly until the superior border of the pancreas is reached. The peritoneum is continuous with the peritoneum investing the gastric side of the gastroesophageal junction. If this layer has not been included with the dissection, the peritoneum must be divided here, exposing the gastroesophageal junction posteriorly. Figure 35-38 demonstrates the stomach completely mobilized except for its attachment to the esophagus. A noncrushing clamp is placed on the mobilized esophagus and the specimen is resected. To minimize spillage of luminal contents, a second clamp is placed on the gastric side or the TA-55 stapler may be fired below the line of resection and above the gastroesophageal junction.
Gastric resection for carcinoma. The esophagus is transected just above the gastroesophageal junction.

Our preferred technique for reconstruction is a simple Roux-en-Y, with an end-to-side esophagojejunal anastomosis with the Roux limb. Using the GIA stapler, a section of jejunum is divided 10 to 15 cm beyond the ligament of Treitz (Fig. 35-39). The Roux limb is brought antecolic up to the esophagus. An enteroenterostomy is constructed between the jejunum on the duodenal side of the Y and the jejunum, 40 to 45 cm distal to the Roux limb staple line (Fig. 35-40). The enteroenteral anastomosis can be performed using hand-sewn two-layer technique or stapling technique. The esophagojejunal anastomosis is performed using interrupted 3-0 silk sutures for both the inner and outer layers, as shown in Figure 35-41, or by the use of an EEA stapler.
The completed reconstruction is shown in Figure 35-42. This figure emphasizes the antecolic position of the anastomosis when the operation is performed for malignant disease. Areas of potential internal herniation in the mesentery are closed with absorbable 3-0 sutures.

**FIGURE 35-39** Gastric insert for carcinoma. Construction of Roux-en-Y limb begins with division of the jejunum beyond the ligament of Treitz.
FIGURE 35-40 Construction of Roux-en-Y anastomosis. The enteroenterostomy is performed in two layers. The length of the Roux limb measures 40 cm.
FIGURE 35-41  Roux-en-Y reconstruction following total gastrectomy. The
anastomosis is prepared using two layers of interrupted 3-0 silk sutures. **A.** Outer layer of posterior sutures. **B.** Site of enterotomy. **C.** Posterior inner row of sutures **D.** Completed esophagojejunal anastomosis.

**FIGURE 35-42** Roux-en-Y reconstruction completed. NG, nasogastric.

A jejunal pouch (Hunt-Lawrence pouch) also may be constructed, with the idea of anastomosing the esophagus in end-to-side fashion with the antimesenteric border of the pouch. The technique is illustrated in Figures 35-43 through 35-45 and can be performed expeditiously using surgical staplers. The pouch is constructed with the goal of providing a
reservoir function. Alternatively, a number of surgeons expressed a preference for leaving an island of undivided intestine at the bend in the pouch. This should theoretically optimize the blood supply to the anastomosis. The circular stapler can be passed through the open end of the Roux limb in order to perform the end-esophagus to side-jejunum anastomosis. The linear stapler then can be fired in such a way as to leave the island of undivided intestine. One important point is that the pouch can be made too long, giving rise to stasis and ineffective clearance of food from the pouch into the intestine. The pouch should not be more than 15 cm in length.
FIGURE 35-43 Total gastrectomy with jejunal pouch reconstruction.

FIGURE 35-44 Total gastrectomy. The circular stapler is positioned via the enterotomies. The center rod is pushed through the antimesenteric border of the jejunum using cautery to prevent tearing.
Laparoscopic Approaches

LAPAROSCOPIC APPROACHES TO THE VAGUS NERVE

As noted previously, the advent of laparoscopic approaches has led surgeons to reconsider traditional approaches to peptic ulcer disease. The advantages of minimally invasive approaches revolve largely around the minimal postoperative discomfort and rapid recovery, with a potential benefit in reduced cost of surgery versus the cost of long-term medication. At the same time, rapid advances have occurred in our understanding of the role of
Helicobacter pylori and mucosal growth, and angiogenic factors in ulcer healing and recurrence. In addition, limitations in access and suturing techniques have increased the difficulty of access to the lesser sac and of performing drainage procedures. These considerations have led surgeons to question the rationale for routine drainage whenever TV has been performed.\textsuperscript{15,37} A number of approaches have evolved to address these difficulties and have been given credibility in the laparoscopic experience. One such approach has been to combine truncal vagotomy with pyloric dilation or seromyotomy.\textsuperscript{26,16,21} Another has been to combine a posterior truncal vagotomy with an anterior highly selective vagotomy or with an anterior seromyotomy.\textsuperscript{16} The important elements of the laparoscopic approach to the vagi are discussed here.

**PATIENT POSITION AND PORT PLACEMENT**

The patient is placed on the operating room table with legs in stirrups and apart (Fig. 35-46). Video monitors are placed on either side at the head; the surgeon often works best when standing between the legs, with the camera operator on the right and the first assistant on the patient’s left. The scrub nurse/technician and instrument table are placed at the patient’s right foot. A large esophageal tube or even a gastroscope is placed in the stomach to facilitate visualization of the distal esophagus. Frequent aspiration of the gastric contents is crucial to maintain total collapse of the stomach and the best visualization. We recommend an open technique to gain access to the peritoneum, insufflating to a pressure of 14 mm Hg. Five ports are placed in the following locations: (1) a 12-mm laparoscope port at the superior edge of the umbilicus or placed 5 cm above and lateral to the left of midline; (2) a 5-mm irrigation/suction and dissection port in the subxiphoid position, just to the right of midline; (3) a 10-mm port for retraction and grasping forceps midway between the umbilicus and xiphoid, to the right of the rectus, and possibly as far as the midclavicular line; (4) a 10-mm port for grasping forceps midway between the umbilicus and xiphoid, almost to the anterior axillary line on the left; and (5) a 12-mm operating port just lateral to the rectus 3 cm above the umbilicus. A number of surgeons prefer the angled 30-degree laparoscope for this operation.
LAPAROSCOPIC TRUNCAL VAGOTOMY

The left lobe of the liver is retracted using a probe placed via the subxiphoid port or the 10-mm fan retractor placed via the higher right-side port (Fig. 35-47). Visualization is improved when tissues from the hiatus are dissected away from the esophagus and lesser curvature (Figs 35-48 and 35-49). One can encounter a coronary hepatic vein or accessory hepatic artery in this dissection. These do not always need to be sacrificed. The right crus of the diaphragm usually is seen here and can be retracted with one of the blades of the liver retractor (Fig. 35-50). A Babcock clamp or other atraumatic grasper...
is used to retract the anterior greater curvature (distal to the cardia) to the patient’s left. A hook coagulator or dissecting forceps is used to incise the lesser omentum, entering the lesser sac just above the takeoff of the hepatic branch of the anterior vagus nerve. A plane is developed between the right crus and the esophagus and continued posteriorly. Continued dissection along the wall of the esophagus reveals the posterior trunk, which is ligated between clips and divided (Fig. 35-51). The excised nerve segment is sent for frozen-section examination. The next step is identification of the anterior vagal trunk(s). The phrenoesophageal membrane usually has been entered and incision is extended toward the left, first by scoring the membrane with scissors and then bluntly pushing away the membrane with a cotton dissector. The visualization of major anterior trunks is often easier in the laparoscopic approach, owing to magnification and excellent video optics. These branches also are ligated and divided between clips (Fig. 35-52), with frozen-section confirmation of the nerve segment. Smaller anterior branches are identified and cauterized after being held away from the esophageal wall. It is possible to dissect tissues on either side of the esophagus for a distance of 5 to 6 cm, thereby ensuring division of any nerve branches to the lesser curvature and cardia. The main difficulty can occur in visualizing the angle of His and possibly missing major vagal branches, including the “criminal nerve.” With the use of a traction forceps placed through the subxiphoid port and a cotton dissector placed via the left grasping forceps, it is possible to expose the left edge of the gastroesophageal junction and cauterize or clip any branches.
FIGURE 35-47  Laparoscopic view of the hiatus.
FIGURE 35-48 Laparoscopic view of the anterior vagus nerve. A. Before dissection. B. After dissection.
FIGURE 35-49 Laparoscopically assisted vagotomy. The gastrohepatic ligament is dissected anteriorly without injury to the vagus nerves.

FIGURE 35-50 Laparoscopically assisted vagotomy. The crus of the
diaphragm is retracted to the patient’s right. The anterior vagal trunk is exposed at the gastroesophageal junction.

**FIGURE 35-51** Laparoscopically assisted vagotomy. The posterior trunk is ligated between clips and divided.
ANTERIOR PROXIMAL VAGOTOMY OR SEROMYOTOMY

A laparoscopic dissection of the posterior leaf is feasible. However, the combination of posterior TV and an anterior selective operation is appealing because it avoids the difficult maneuver of working through the lesser sac in order to visualize the posterior lesser omentum and nerves accompanying the ascending left gastric artery branches. For HSV, dissection is begun at the crow’s foot, approximately 6 cm from the pylorus. Retraction of the greater curvature is performed using a Babcock clamp (Fig. 35-53). With the magnification available through the scope, the proximal branch of the crow’s foot is often, but not always, relatively easy to identify. The anterior leaf of the lesser omentum is approached by dividing and ligating the neurovascular bundle between clips. Electrocautery is used sparingly, and preferably not at all. The serosa overlying the gastroesophageal junction is scored as in the open procedure. Dissection of the distal 5 cm of esophagus and cardiac branches is carried out as described previously for TV.
The goal of an anterior seromyotomy, as described originally by Taylor et al.\textsuperscript{65} and then others,\textsuperscript{13,26,66} is to sever the neurovascular bundles dividing the serosa and muscularis that transmit these nerves to the mucosa. The anterior surface of the stomach is retracted using the right and left grasping ports. The outline of the seromyotomy is scored using a coagulator hook or spatula, on the anterior surface of the stomach, 1 cm from the visible border of the lesser curvature. Moving caudad and parallel to the lesser curvature, a line is traced from the gastroesophageal junction to the first branch of the crow’s foot, or arbitrarily 6 cm from the pylorus. The hook coagulator is most suitable for performing the seromyotomy, using monopolar current for electrocoagulation. The hook cuts through successive layers of gastric wall, the serosa, outer oblique muscle fibers, middle longitudinal fibers, and inner circular fibers. The two grasping ports then are used to place traction on the two edges of the gastric wall, exposing the deep circular fibers that may split as much from traction as from cautery. The darker submucosa/mucosa layer
pops through the muscularis. This layer is inspected for any evidence of full-thickness cautery injury or perforation. With a complete seromyotomy, the gap between the cut edges should be about 6 to 8 mm. Alternatively, a laparoscopic surgical stapling device can be used for creation of a modified seromyotomy.\textsuperscript{26}

A number of decent-sized vessels may be encountered in the dissection. Prolonged cauterization may provide hemostasis but risks a full-thickness burn and subsequent perforation. The hook can be used to isolate these vessels and lift them for clipping in continuity. Recent advances in the design of needle holders may make it possible to suture these vessels in continuity before division by scissors. Surgical stapling devices can be used for this purpose as well as newer devices such as the harmonic scalpel, which utilizes ultrasonic energy for coagulating vessels, or electrothermal bipolar coagulator devices. After creation of the seromyotomy, the integrity of the mucosa should be verified by moderate expansion of the stomach using the NG tube for insufflation. Some authors use methylene blue solution (1 vial per 200 mL), placed intragastrically, for this maneuver. The seromyotomy then is closed using a continuous suturing technique. A tongue of omentum may be mobilized and secured over the seromyotomy as a patch, secured with sutures placed through either edge of the seromyotomy.

**MINIMALLY INVASIVE APPROACHES TO GASTRIC RESECTION**

The patient is positioned the same way as for laparoscopic antisecretory surgery, with the patient supine with legs in stirrups and apart as shown in Figure 35-46. Port placement is similar with five ports placed in the following locations: (1) a 12-mm laparoscope port at the superior edge of the umbilicus or placed 5 cm above and lateral to the left of midline; (2) a 12-mm port in the right midclavicular line; (3) a 12-mm port in the left midclavicular line; (4) a 5-mm port for grasping forceps at the anterior axillary line on the left; and (5) a 5-mm port almost at the anterior axillary line on the right. A 30- or 45-degree angled laparoscope is useful for gastric resections, as it allows improved visualization of the stomach from multiple perspectives. If resections high in the lesser curvature are planned, retraction of the left lobe of the liver using a probe placed via the subxiphoid port or the 10-mm fan retractor placed via the higher right-side port (see Fig. 35-51) is useful as
described for laparoscopic TV.

Wedge resections of benign but symptomatic masses on the greater curvature can be done by grasping the greater curvature with a Babcock or other atraumatic grasper and use of a laparoscopic stapling device to resect the involved portion of stomach. Occasionally intraoperative endoscopic confirmation of the position of intraluminal masses not readily apparent intraoperatively is useful. Wedge resections on the lesser curvature are more difficult due to the presence of the left lobe of the liver, which usually needs to be retracted, and the proximity of the esophagus and vagus nerves. However, with careful attention to the gastroesophageal junction, wedge resections of the lesser curvature can be done. Intraluminal approaches can also be utilized. If the vagus nerve or its major branches are sacrificed in lesser curvature resections, a laparoscopic or endoscopic drainage procedure is recommended (endoscopic pyloric dilation or laparoscopic pyloric seromyotomy). Robotic-assisted gastric wedge resections may be performed in a similar manner, although the wristed instrumentation also allows for ease in circumferentially obtaining a full-thickness resection. The authors prefer to perform this resection with cauterized shears, and to repair the defect with a two-layer suture closure (Fig. 35-54).

FIGURE 35-54 Robotic view of gastric wedge resection. A. Development of the wedge. B. Excision and margins prior to closure. C. Two-layer suture closure with braided absorbable suture for the outer layer (or absorbable monofilament).

Distal, subtotal, and total gastrectomy procedures have all been adapted for laparoscopic or, more recently, robotic approaches. With advances in equipment and concentrated experience, all approaches seem to be finding increasing application, with promising results in selected patients. In minimally-invasive subtotal or total gastrectomy, port placement is similar to
that for wedge resections and antisecretory procedures (Fig. 35-55). Gastric mobilization, resection, and reconstruction are done in a similar fashion to that of the open procedures, although en bloc resections are typically not performed. After entry into the abdominal cavity and port placement, the left lobe of the liver is retracted laterally with a fan retractor or probe through the right lateral port if the lesser curvature cannot be adequately visualized or if extensive dissection of the lesser curvature is required. With a robotic approach, the third arm can often be utilized for liver retraction. The stomach is grasped with a laparoscopic Babcock clamp, and the distal stomach is mobilized by incising the gastrocolic ligament, which is taken with the harmonic scalpel or electrothermal bipolar coagulator device. The dissection is carried distally along the greater curvature to the duodenal bulb, dividing the small branches of the gastroepiploic artery to the gastric wall, similarly with the harmonic scalpel or electrothermal bipolar coagulator device. The duodenal bulb can be dissected away from the anterior aspect of the pancreas, allowing for circumferential clearance. Proximal dissection is carried out in a similar way, with division of the short gastric vessels until the left diaphragmatic crus is visualized, in the case of a total gastrectomy. Others have used endoscopic vascular staplers to take much of gastrocolic omentum and its vessels. Once the proximal portion of the gastric dissection is reached, the stomach is divided with laparoscopic staplers at our institution. The gastric resection is then completed by division of the distal stomach just past the pylorus with a laparoscopic stapler. An omentectomy is then performed, with mobilization of the omentum off of the transverse colon utilizing cautery or the electrothermal bipolar coagulator device. Reconstruction is completed as a B-II gastrojejunostomy. Babcock clamps are used to locate the jejunum at the ligament of Treitz and bring a freely mobile portion of jejunum, typically 20 to 30 cm distal to the ligament of Treitz, up to the proximal gastric remnant in an antecolic or retrocolic fashion through an avascular window in the transverse colon mesentery. The gastric remnant and jejunum are aligned together, being careful not to twist the jejunal mesentery, and then secured to each other at the proximal and distal suture lines by interrupted 3–0 Vicryl sutures placed either with an Endo Stitch (Auto Suture Company, Norwalk, CT) or with a laparoscopic needle driver. After the gastric and jejunal limbs are aligned, Bovie cautery is used to place enterotomies in the proximal gastric remnant and jejunum. It is the author’s preference that a retrogastric anastomosis be created, with approximation of
the jejunum to the posterior wall of the stomach. A laparoscopic stapler is placed into the gastric and jejunal limbs and then deployed to form the anastomotic staple line. The proximal portion of the anastomosis is then closed using a laparoscopic stapler or suture-closed using an Endo Stitch device or with a laparoscopic needle driver. For total gastrectomy, the esophagojejunal anastomosis is performed using the stapling device as illustrated in Figure 35-56. The mesenteric defect in the transverse colon is then closed if a retrocolic anastomosis has been performed. For total gastrectomy, a laparoscopic feeding jejunostomy tube is also placed, generally 10 cm distal to the jejunoojejunostomy anastomosis.
FIGURE 35-55  Port placement for laparoscopic subtotal or total gastrectomy.
FIGURE 35-56  Schematic view of laparoscopic total gastrectomy. The esophagojejunal anastomosis is performed using the stapling device.

Laparoendoscopically Assisted Sentinel Node Navigation

One of the concerns with laparoscopic gastrectomy procedures, done in patients with gastric cancer, is to determine whether a radical lymphadenectomy would be required. For early-stage gastric lesions (clinical and radiologic stage T1N0), sentinel node identification and so-called “sentinel node navigation” of the operation\textsuperscript{71–73} have been advocated. Both single- and double-tracer methods have been described.\textsuperscript{74} For complementary tracer injection, a method similar to that described recently by Orsenigo et al. would be utilized.\textsuperscript{75,76} On the day prior to operation, endoscopy is performed to inject radioactive tracer (\textsuperscript{99}Tc-colloid, 2 mL total) at four equally spaced points in direct proximity to the tumor; at the beginning of the actual operation, blue dye (2% patent blue, 2 mL divided among four sites) is injected endoscopically. The accumulation of radioactive tracer in the nodal
basin occurs over a period of 2 to 20 hours, while the transfer of blue dye to the sentinel node occurs very quickly. As a result, the sentinel node seems reliably identified when the blue node contains at least 10-fold higher radioactive counts than background. It has been suggested that the radical lymphadenectomy may be limited to a D1 dissection if the sentinel node is clearly identified and clearly negative, but long-term outcomes in controlled trials are not yet fully known.

Minimally Invasive Lymphadenectomy

Modified D2 lymphadenectomy, excluding the routine resection of the distal pancreas and spleen, has become standard of care in gastric resections for cancer, per recent National Comprehensive Cancer Network guidelines. Increasing experience with minimally-invasive techniques has decreased the morbidity previously associated with lymphadenectomy. The author’s preference is for a robotic approach, with its enhanced optics, which gives the operator an ability to skeletonize the celiac axis and named vascular branches of lymphatic tissue with greater dexterity than the laparoscopic approach as well as the ability to ligate the left gastric artery at its origin from the celiac axis (Fig. 35-57). Experienced laparoscopic surgeons, however, can achieve similar results.

**FIGURE 35-57** Robotic view of the celiac axis during lymphadenectomy with ligation of the left gastric artery. **A.** isolated left gastric artery before division **B.** View of origin of the celiac axis after division of the left gastric
REFERENCES


The human life expectancy has steadily increased over the past few centuries; however, the current generation may be the first with a shorter life expectancy than their parents. The reason behind this unfortunate reversal is not increasing cancer rates or development of resistant bugs or new viruses, but a global increase in obesity and associated comorbidities.\textsuperscript{1}

Obesity is defined as an excess accumulation of body fat and is commonly defined as a body mass index (BMI) of $>30 \text{ kg/m}^2$. In the United States, obesity affects 40\% of women, 35\% of men, and 17\% of children and adolescents. In 2014, there were 600 million obese patients worldwide, with several countries having obesity rates greater than those in the United States. The highest rates of obesity can be found in some of the Pacific Island nations where obesity rates are greater than 40\%. Obesity has been classified into several subcategories, as summarized in Table 36-1, with estimated prevalences from the National Health and Nutrition Examination Survey
Severe obesity is often regarded as BMI ≥40, or ≥35 with obesity-related comorbidities. Superobesity is defined as a BMI ≥50.

<table>
<thead>
<tr>
<th>BMI</th>
<th>Classification</th>
<th>US Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30</td>
<td>Obesity</td>
<td>37.7</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>Class I obesity</td>
<td>30</td>
</tr>
<tr>
<td>35.0-39.9</td>
<td>Class II obesity</td>
<td>7.7</td>
</tr>
<tr>
<td>≥40.0</td>
<td>Class III obesity (morbid)</td>
<td>5.5</td>
</tr>
</tbody>
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With the growing obesity epidemic, there has also been an increase in the prevalence of morbid obesity over the past decade, with a linear growth in the rate of morbid obesity in women.

Although BMI is easy to calculate and has become the universally accepted measure for defining and classifying obesity, it is not ideal and has several limitations because it does not directly measure excess fat accumulation. As a result, a 70-inch muscular and fit athlete who weighs 215 pounds and has a BMI of 31 will be regarded as obese even though they have little excess fat accumulation. Although one can define obesity as percent body fat >32% in women and >25% in men, these calculations are difficult. More importantly, neither BMI nor percent body fat calculations provide any information on the regional body fat distribution. This is important because intra-abdominal and visceral obesity is associated with greater risk of insulin resistance, hyperlipidemia, hypertension, cardiovascular disease (CVD), and stroke than peripheral fat distribution. This difference is important because those with central obesity (android or apple pattern of obesity) have a greater risk of diabetes and CVD than those with fat accumulation in the subcutaneous tissue of buttock areas (gynoid or pear pattern of obesity). This difference in fat distribution may explain why individuals of Asian origin have a greater risk of diabetes at a lower BMI. As a result, many have proposed lowering the BMI threshold at which weight management interventions, including surgery, are recommended in this population group.

The global epidemic of obesity is multifactorial and has genetic,
environmental, and epigenetic roots. It is thought that the recent exposure of man to an environment with excess and readily available food leads to an imbalance between caloric intake and energy expenditure, resulting in excess fat deposition. The reduction in physical activity and our new sedentary lifestyle have a significant role to play in the current obesity epidemic. Obesity is strongly and inversely related to degree of moderate physical activity, with small changes in daily levels of moderately vigorous physical activity leading to large differences in risk of obesity. Of all sedentary behaviors, prolonged television (TV) watching appears to be the most predictive of obesity and diabetes risk. In the Nurses’ Health Study, after adjustment for age, smoking, exercise level, and dietary factors, every 2-hour increment spent watching TV was associated with a 23% increase in obesity and a 14% increase in the risk of diabetes. The detrimental effect of TV on weight is in large part due to frequent snacking while watching TV and the associated increase in calorie intake, rather than decrease in physical activity alone.

Many studies have also confirmed that genetic factors influence obesity. In a meta-analysis of genomewide association studies (GWAS) and Metabochip studies involving nearly 34,000 patients, 97 loci were identified that were associated with BMI and accounted for approximately 2.7% of BMI variation. The GWAS analysis suggested that common variation accounts for about 21% of BMI variation. Thus, although in rare cases such as leptin deficiency, a genetic mutation may be the primary factor in the development of obesity, the more common situation is where susceptibility genes interact with environmental factors to predispose individuals to obesity. As an example, in a recent study of nearly 9000 people, the association between BMI and a polygenic risk score was higher in recent birth cohorts compared with earlier birth cohorts, likely due to the earlier exposure of the more recent cohort to our “obesogenic” environment.

**ADVERSE CONSEQUENCES OF OBESITY**

Although there is ongoing debate as to the etiology of the current obesity epidemic, there is little doubt over its adverse impact on health, quality of life, and life expectancy, with individuals who have a BMI >40 having a reduced life expectancy of 8 years. The adverse effect of obesity on mortality
rate has been confirmed in differing population cohorts across the world where each 5-unit increase in BMI increased mortality rate by 39% in Europe, 29% in North America, 39% in East Asia, and 31% in Australia and New Zealand. For the 4 populations combined, all-cause mortality risk increased with increasing BMI when compared to individuals with a BMI between 22.5 and 25 as baseline: 7% for BMI of 25.0 to <27.5, 20% for BMI of 27.5 to <30.0, 45% for BMI of 30.0 to <35.0, and 94% for BMI of 35.0 to <40.0.\(^8\)

The increase in mortality in obese individuals is due to increased risk of many serious and chronic conditions including type 2 diabetes, heart disease, hypertension, stroke, hyperlipidemia, cancer, and sleep apnea (Table 36-2). The prevalence of these comorbidities often increases even with modest further weight gain. This observation is most striking when looking at type 2 diabetes. Compared with women with stable weight and after adjusting for age and BMI, the relative risk for diabetes mellitus increased 2-fold in women who had a weight gain of 5.0 to 7.9 kg and increased by 3-fold in those who gained 8.0 to 10.9 kg.\(^9,10\)

TABLE 36-2: RISKS OF CARDIOVASCULAR AND METABOLIC DISORDERS WITH OBESITY\(^{10}\)
Metabolic Syndrome

The observation that central obesity, with or without excess total body weight, and associated hypertension, hyperlipidemia, and insulin resistance can increase risk of CVD and diabetes suggested the existence of a “metabolic syndrome.” This syndrome has also been known as syndrome X.
or obesity dyslipidemia syndrome. Several differing definitions have been used for this condition, as summarized in Table 36-3.11

<table>
<thead>
<tr>
<th>Required</th>
<th>NCEP ATP III</th>
<th>IDF</th>
<th>WHO</th>
<th>EGIR</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of additional abnormalities</td>
<td>≥3 of:</td>
<td>and ≥2 of:</td>
<td>and ≥2 of:</td>
<td>and ≥2 of:</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose</td>
<td>≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes</td>
<td>6.1-6.9 mmol/L (110-125 mg/dL)</td>
<td>≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)</td>
<td>≥1.0 mmol/L (40 mg/dL) (men); &lt;1.3 mmol/L (50 mg/dL) (women)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (HDL-C)</td>
<td>&lt;1.0 mmol/L (40 mg/dL) (men); &lt;1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C</td>
<td>&lt;1.0 mmol/L (40 mg/dL)</td>
<td>&lt;0.9 mmol/L (35 mg/dL) (men); &lt;1.0 mmol/L (40 mg/dL) (women)</td>
<td>&lt;1.0 mmol/L (40 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides</td>
<td>≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides</td>
<td>≥1.7 mmol/L (150 mg/dL)</td>
<td>≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia</td>
<td>≥1.7 mmol/L (150 mg/dL)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Waist ≥102 cm (men) or ≥88 cm (women)</td>
<td>Waist ≥80 cm (men) or ≥85 cm (women) or BMI ≥30 kg/m²</td>
<td>Waist ≥94 cm (men) or ≥80 cm (women)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>≥130/85 mm Hg or drug treatment for hypertension</td>
<td>≥130/85 mm Hg or drug treatment for hypertension</td>
<td>≥140/90 mm Hg</td>
<td>≥140/90 mm Hg or drug treatment for hypertension</td>
<td>≥130/85 mm Hg</td>
</tr>
</tbody>
</table>

**TABLE 36-4: ETHNIC-SPECIFIC WAIST CIRCUMFERENCE VALUES FOR THE INTERNATIONAL DIABETES FEDERATION DEFINITION OF METABOLIC SYNDROME**

Abbreviations: AACE, American Association of Clinical Endocrinologists; EGIR, European Group for the Study of Insulin Resistance; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition of metabolic syndrome is the most widely used, whereas the International Diabetes Federation (IDF) defines it as increased waist circumference, with ethnic-specific waist circumference cut points (Table 36-4).
The estimates on the prevalence of metabolic syndrome can thus vary based on definition used and population studied. For example, using the NHANES 1999 to 2002 data, approximately 35% of the population met the NCEP ATP III definition of metabolic syndrome, but this increased to 39% using the IDF definition. The prevalence of the syndrome increases with increasing BMI. Whereas 5% of normal-weight individuals have metabolic syndrome, the risk increases to 60% for those with BMI >30.\textsuperscript{12}

Despite the extensive literature on metabolic syndrome, many have raised questions about the use of this term and whether it captures a unique pathology, as implied by calling it a “syndrome,” and whether it confers CVD risk beyond its individual components. These questions have raised uncertainty and debate about the value of this diagnosis. Regardless of whether it is a unique syndrome or just a collection of several known risk factors associated with excessive visceral fat, we now know that the driver of the underlying pathology is the chronic inflammatory state associated with excess accumulation of adipose tissue in liver, muscle, and adipose tissue stores. Although adipose tissue was originally thought to be a relatively quiescent accumulation of stored calories, it is now known that adipose tissue is metabolically active and can be the source of many adipocyte-derived peptides (eg, leptin, adiponectin, resistin) and cytokines (eg, tumor necrosis factor-α, interleukin-6), collectively referred to as adipokines. The actions of these agents lead to a state of chronic inflammation, which in turn interferes with many physiologic cellular processes (eg, insulin signaling), and cause vascular endothelial dysfunction and vascular inflammation, leading to the development of atherosclerotic CVD.

The cornerstone of treatment for patients diagnosed with obesity and metabolic syndrome has been risk reduction in the form of weight loss, increased exercise, and treatment of associated diabetes, hypertension, and hyperlipidemia.
Although modest weight loss (5%-10% excess weight) can lead to reductions in the risk of these chronic diseases, achieving durable weight loss is challenging, especially as the degree of obesity increases. Current approaches to weight loss are covered in the following sections.

**APPROACHES TO WEIGHT LOSS**

**Diet and Lifestyle**

Regarded as the cornerstone of weight management, the essential element of all diets is a reduction in caloric intake. The usual goal is to restrict caloric intake to 1200 to 1500 calories for women and 1500 to 1800 calories for men. Although multiple diets have been promoted, there is little evidence that one is superior to the other. In a study of 811 patients assigned to 4 diets with differing carbohydrate, protein, and fat compositions, the weight loss at 2 years was similar between the groups, as were satiety, hunger, and satisfaction with the diet. Importantly, the weight loss with dieting alone is modest. In fact, in studies in which the dieting was not supervised or supported, the weight loss was often insignificant (1-2 kg). With increased intensity of support and follow-up (either in person or virtual), weight loss can be improved, with approximately one-third of patients achieving a meaningful 5% reduction in total body weight during the study period. The absolute average weight loss, however, remains modest at 4 to 5 kg and is often not sustained once the follow-up and support are removed.

Exercise and increased activity are another important component of lifestyle modification that is recommended. General recommendations are to increase daily activity to >10,000 steps per day and perform >150 minutes of aerobic physical activity per week. However, the data on the additional impact of exercise on weight loss are surprisingly modest, with a meta-analysis comparing diet alone to diet and exercise program, showing that pooled weight loss was only 1.14 kg greater for the diet-plus-exercise group than the diet-only group. This highlights the importance of dieting and reducing caloric intake. However, the addition of exercise brings about related health benefits and can play an important role in weight loss maintenance, when dietary adherence may be less strict.
Weight Loss Medications

For those with need and desire to lose a greater percentage of their weight, there is an increasing list of available medications, with 4 US Food and Drug Administration (FDA)-approved weight loss medications entering the market over the past 5 years. Prescribing these medications requires detailed knowledge of the medication and mode of action, as well as the potential side effects and interactions with other medications that patients may be taking. Bariatric surgeons are becoming increasingly familiar with prescribing these medications, allowing them to offer their patients a more diverse and tailored weight management option. Pharmacotherapy can be initiated in patients with BMI >30 or BMI >27 with related comorbidities and is being increasingly used in patients with inadequate weight loss or weight regain after bariatric surgery. These medications can help increase compliance with low-calorie diets by suppressing hunger and increasing satiety.

Table 36-5 provides a summary of current FDA-approved agents.\textsuperscript{15,17} Usual practice is to try a medication for 3 months and, if significant weight loss is not seen, discontinue and try an alternative.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|}
\hline
Generic Drug Name (Trade Name) & FDA Approval & Mode of Action & TBWL\% & Side Effects \\
\hline
Phentermine & 1959 & Adrenergic agonist that stimulates sympathetic nervous system, thus increasing basal metabolic rate and reducing appetite & 5\%-6\% & Dizziness, dry mouth, irritability, difficulty sleeping \\
Oxilat (Xenical or Alli) & 1999 & Inhibits pancreatic and gastric lipase, causing fat malabsorption & 5\%-10\% & Diarrhea, fecal incontinence, flatulence \\
Lorcaserin (Belviq) & 2012 & Serotonin receptor agonist that reduces food intake by selectively activating POMC neurons in the hypothalamus & 5\%-7\% & Headache, hallucination, heart valve damage \\
Phentermine-topiramate (Qsymia) & 2012 & Norepinephrine/dopamine reuptake inhibitor and \(\gamma\)-aminobutyric acid (GABA) receptor agonist & 7\%-10\% & Headache, paresthesia, dry mouth, cleft palate \\
Roxicon SR-naltrexone SR (Contrave) & 2014 & Bupropion: dopamine/norepinephrine reuptake inhibitors; naltrexone: opioid receptor antagonist & 5\%-6\% & Headache, insomnia, constipation, tremor \\
Liraglutide (Saxenda) & 2014 & Glucagon-like peptide-1 receptor agonist that works by reducing appetite, increasing satiety, and delaying gastric emptying & 7\%-9\% & Diarrhea, nausea, pancreatitis \\
\hline
\end{tabular}
\caption{FDA-APPROVED DRUGS FOR WEIGHT MANAGEMENT}
\end{table}

Abbreviation: TBWL\%, total body weight loss percentage.

Phentermine was introduced in 1959 and became part of the drug combination “fen-phen” that was ultimately withdrawn from the market in
1997 due to the heart valve disease caused by the fenfluramine component of the formulation. Phentermine is approved for short-term use (3 months), with most weight loss being observed in the first few weeks.

Orlistat was the only FDA-approved weight loss medication until 2012, but its gastrointestinal side effects limited tolerability in many patients. However, in patients with obesity and baseline constipation, it can be an attractive option.\textsuperscript{18}

Lorcaserin, at the recommended dose, is a selective 5-HT\textsubscript{2c} receptor agonist that is thought to reduce food intake and increase satiety by selectively activating these receptors on anorexigenic proopiomelanocortin (POMC) neurons in the hypothalamus. Activation of other serotonin receptors, specially 5-HT\textsubscript{2a} and 5-HT\textsubscript{2B}, can lead to the side effects associated with the drug, including hallucinations and possible heart valve disease.\textsuperscript{19}

Phentermine-topiramate is another combination drug containing phentermine. The other ingredient, topiramate, was originally approved for migraine and epilepsy but was also noted to reduce food intake.\textsuperscript{20}

Bupropion slow release (SR)-naltrexone SR is another combination drug containing 2 agents that have been on the market for many years but for different indications: bupropion for depression and naltrexone for opiate dependency and alcohol addiction. The drugs work in a synergistic fashion to release hypothalamic release of α-melanocyte–stimulating hormone, a potent anorectic neuropeptide.\textsuperscript{21}

Liraglutide was approved in 2010 for the treatment of type 2 diabetes but was also found to cause weight loss in a dose-dependent manner. This led to the approval of the drug at a higher dose of 3.0 mg for management of obesity. The drug is administered as a daily subcutaneous injection, starting at a low dose with weekly dose escalation.\textsuperscript{22}

**Endoluminal Therapies and Alternative Devices**

To address the need of many in whom diet, lifestyle modifications, and/or medications have been unsuccessful in achieving meaningful weight loss, gastrointestinal innovators have developed many endoscopic devices with the goal of achieving greater weight loss while avoiding the uneasiness of surgery.
Table 36-6 provides an overview of the FDA-approved endoluminal devices. Intragastric balloons, the most commonly used devices, have a long history that dates back to the Garren-Edwards bubble, which was approved by the FDA in 1985 but subsequently withdrawn from the market in 1988 due to increasing rates of complications. Over the subsequent years, balloon designs have evolved with improved safety and efficacy. There are currently 3 different FDA-approved intragastric balloons for patients with BMI of 30 to 40; duration of use is 6 months, after which they need to be removed. The Orbera and ReShape balloons are endoscopically placed and removed, whereas the Obalon system, which consists of 3 smaller balloons placed at 2-week intervals using fluoroscopy, only requires an endoscopy for removal. Main side effects are gastrointestinal related and include nausea, vomiting, abdominal pain, reflux, and burping. Serious adverse events related to the balloon have also been reported. Balloons, especially those not removed on time, can rupture with balloon migration and possible bowel obstruction. With increasing utilization of the balloons, cases of spontaneous overdistention and acute pancreatitis have also been reported, and an FDA warning was recently issued. Regaining of lost weight is a common problem in patients after balloon removal, although some studies have suggested that with continued diet and exercise, some weight loss can be maintained for up to 5 years after removal.

![Table 36-6: FDA-Approved Endoluminal Devices for Management of Obesity](image)

<table>
<thead>
<tr>
<th>Device Name</th>
<th>FDA Approval</th>
<th>Mode of Action</th>
<th>TBWL%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbera intragastric balloon</td>
<td>2015</td>
<td>Space-occupying devices that produce early satiety and delay gastric emptying</td>
<td>7%-15%</td>
<td>Approved for 6-month use in those with BMI of 30-40</td>
</tr>
<tr>
<td>ReShape dual intragastric balloon</td>
<td>2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obalon intragastric balloon</td>
<td>2016</td>
<td>Aspirate ingested food intake and modify eating habits</td>
<td>10%-15%</td>
<td>Approved for BMI of 35-55</td>
</tr>
<tr>
<td>Aspire Assist</td>
<td>2016</td>
<td>Reducing gastric volume</td>
<td>15%-20%</td>
<td>A commercially approved endoscopic suturing platform is used to perform the endoscopic suturing</td>
</tr>
<tr>
<td>Endoscopic sleeve gastroplasty</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; TBWL%, total body weight loss percentage.

The Aspire Assist device consists of a gastrostomy tube (A-tube) attached to a port, which is used to aspirate gastric contents 20 to 30 minutes after
eating a meal. The device is approved for patients with BMIs up to 55 and can be used long-term. Some believe the device may have a role as a bridge to a more definitive weight loss intervention, by helping patients with high BMI achieve significant preoperative weight loss. Main side effects include abdominal pain, nausea and vomiting, tube blockage, granulation and irritation at the tube site, and risk of gastrocutaneous fistula after tube removal.

Endoscopic sleeve gastroplasty is an endoscopic procedure in which a sleeve-like gastric conduit in a created, similar to a sleeve gastrectomy. A series of endoscopic full-thickness sutures are placed endoscopically using a commercially available suturing device (Overstitch; Apollo Endosurgery) to create a narrowed gastric conduit with reduced gastric volume. Several serious adverse events have been reported with this procedure, including perigastric collections requiring interventional radiology drainage and self-limited splenic hemorrhage.

Another FDA-approved obesity device is the VBLOC system. Unlike the procedures summarized in Table 36-6, this device is placed laparoscopically under general anesthesia as an outpatient surgical procedure. The system consists of a subcutaneously placed neuromodulator, connected via 2 electrodes placed laparoscopically around the anterior and posterior vagal trunks. Several studies have shown an 8% to 10% total body weight loss with this procedure, which was superior to controls. The device received FDA approval in 2015 for patients with a BMI of 35 to 45 with at least 1 other obesity-related condition, such as type 2 diabetes. The serious adverse event rate with the device is low and reported at <5%, with 1 case of gastric perforation at the time of device removal.

Although medications and described devices may adequately address the needs of patients with stage I obesity, for those with more significant obesity, bariatric surgery has become the standard of care. The next chapter of this book will provide a detailed review of the technical aspects of various surgical techniques available. All procedures lead to durable and meaningful weight loss, which leads to significant improvements in many comorbidities. Table 36-7 summarizes treatment recommendations based on patients’ BMI as proposed by the American Heart Association/American College of Cardiology/The Obesity Society Obesity Guideline and supported by the American Gastroenterological Association’s Practice Guide on Obesity and
Weight Management, Education, and Resources.\textsuperscript{15,28}

TABLE 36-7: WEIGHT MANAGEMENT RECOMMENDATIONS BASED ON PRESENTING BMI AND COMORBIDITIES

<table>
<thead>
<tr>
<th></th>
<th>BMI 25-27</th>
<th>BMI 27-30</th>
<th>BMI 30-35</th>
<th>BMI 35-40</th>
<th>BMI &gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>+ if risk factors\textsuperscript{a}</td>
<td>+ if risk factors\textsuperscript{a}</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>+ if risk factors\textsuperscript{a}</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bariatric endoscopy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>+ if comorbidities\textsuperscript{b}</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Such as cardiovascular disease risk factor (diabetes, prediabetes, hypertension, dyslipidemia, increased waist circumference) or other obesity-related conditions.

\textsuperscript{b}Including diabetes, hypertension, or sleep apnea.

Despite such guidelines highlighting the role of surgery in weight management, only 1% to 2% of patients who qualify for weight loss surgery proceed with the operations. The reasons behind this low rate are unclear and likely multifactorial. Insurance barriers, access to appropriate surgical expertise, and provider and patient bias toward obesity management and surgery play a role. Another important factor is that the invasiveness of surgery, permanent change to gastrointestinal anatomy, and risk of weight regain and surgical complications dampen the enthusiasm of many to proceed with surgery. This will continue to be the driving engine behind further innovation and development in gastrointestinal-based interventions for treatment of obesity.

REFERENCES

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SURGICAL TREATMENT OF MORBID OBESITY AND TYPE 2 DIABETES

Bruce D. Schirmer

INTRODUCTION

The surgical treatment of obesity originated with the concept that a surgical intervention to alter digestive anatomy and physiology could benefit patients with a metabolic related disease. At the University of Minnesota in the 1950s, surgeons performed an operation to bypass the distal small bowel to limit absorption of lipids in a patient with severe hyperlipidemia.\(^1\) Over 60 years later, the field of metabolic and bariatric surgery has evolved to provide increasingly safe and effective surgical treatment options for patients who suffer the consequences of severe metabolic disease, such as type 2 diabetes mellitus. As these treatments have evolved, there has been a concurrent improved understanding of the physiology underlying the diseases being targeted. This has often been a result of the observations of treatment effects of surgical procedures. Increased insight and knowledge have also arisen as a result of trying to better understand how these interventions can be optimally
used for disease treatment. The comorbid metabolic diseases that arise secondary to morbid obesity are generally much better understood than the actual disease of obesity itself. Consequently, surgical treatment has to date focused more on the improvements and resolution of those diseases rather than the disease of obesity. The major manifestation of the disease of obesity, weight itself, certainly has been the focus of bariatric surgery. However, the underlying genetic, physiologic, and metabolic factors that contribute to create the obesity disease state are still not well understood. Hence, surgical therapy has focused on weight as the parameter for treating the disease, while underlying causes are still not directly targeted. Indeed, as investigation continues as to the etiologies of the disease of obesity, surgical therapy may have a more limited role in the future. However, at this time it remains the single most effective treatment for reversing the disease, both in terms of the obvious problem of weight itself as well as the comorbid medical problems that accompany the disease in varying frequency from individual to individual.

The metamorphosis of the surgical patient who has had a successful bariatric operation and has changed from an individual literally burdened by diseases of—and related to—obesity is a dramatic and rewarding phenomenon. Metamorphosis is a truly accurate word to describe this therapeutic change. The massive improvement in quality of life, in physical, mental, and social areas, causes most patients who experience this process to be almost reborn in the true sense of the word. They are relieved of physical pain, social stigmatism, lifestyle limitations, low self-esteem, and a variety of other negative consequences of the obesity state with its concurrent problems. Often the simple fear of imminent death from obesity-related diseases, and the relief that treatment has allowed them to have a chance to live longer is a powerful aspect of treatment success.

The metamorphosis of the surgical patient who has undergone an operative procedure with successful weight loss and resolution or improvement of comorbid medical problems is joyful and dramatic. However, the patient who, after having achieved this success, then relapses into the obesity state through regain of weight and return of metabolic diseases, is equally tragic. To date surgery has been unsuccessful in optimally treating the latter patient, who represents perhaps 20% to 40% of patients who undergo surgical therapy for morbid obesity, depending on the procedure and nature of the diseases. Current surgical therapy is highly
effective in treating the results of the disease of obesity: excess weight and the medical problems that result. This will be well illustrated in the text to follow. However, the reader is reminded that current surgical therapy is also not designed to eliminate the disease of obesity itself, a disease that is still poorly understood in terms of its etiology.

**BRIEF HISTORY OF BARIATRIC SURGERY**

Bariatric surgery emanated from the need to control a severe metabolic problem. In 1954 in Minneapolis, Drs. Kremen and Linner performed the first jejuno-ileal bypass in a human to control hyperlipidemia. This case and a number of others were reported in the first series in the literature in 1963 by Payne. The operation proved effective for treating that problem but caused a variety of malabsorptive and nutritional issues that proved to be unacceptable for all but the most severe cases of hyperlipidemia. Now, six decades later, the field of bariatric surgery is once more turning to the metabolic benefits of operative procedures as the main focus of further research and development of the field. Thus the appropriate appellation for the field is now metabolic and bariatric surgery.

Few bariatric operations were done in the 1960s. When Mason and Ito first described the gastric bypass in 1969, the first and longest-lasting bariatric procedure was launched. After modification by Griffen to drain the gastric pouch using a Roux limb (Fig. 37-1), the procedure became alternatively the most or second most popular metabolic and bariatric operation from then until now. The history of bariatric surgery is one largely of those operations that have come and gone during the past five decades, while the Roux-en-Y gastric bypass (RYGB) has remained in use and provided effective results.
FIGURE 37-1 Roux-en-Y gastric bypass as described by Griffen, modified from Mason.

In the 1970s, the jejunoileal bypass was initially popular, then abandoned due to its occasional production of progressive and lethal hepatic failure. The damage to the reputation of the field of bariatric surgery from the backlash to the poor results of the jejunoileal bypass was felt for the next 25 years. Restrictive-only operations were thereafter viewed as much safer and more appropriate. While the gastric bypass did have a mild element of malabsorption, it was primarily a restrictive operation. Stomach stapling of various configurations was next performed, with all of them proving
ineffective at maintaining adequate restriction for the long term if simple staple lines with gaps or gastric to gastric anastomoses were employed. In the 1980s, the vertical banded gastroplasty (VBG) (Fig. 37-2) was introduced, also by Mason, for the purposes of providing an operation with a durable anatomic configuration that was solely restrictive.\(^5\) The operation had a decade of success before it became apparent that patient adaptation to the restriction, which was to adopt a new diet of high-calorie liquids, usually defeated the operation in the long term.\(^6\) Stenosis of the outflow caused further need to revise the operation, to the point where most have now probably been converted to gastric bypass or other procedures.

**FIGURE 37-2** Vertical banded gastroplasty.

Bariatric surgeons began to perform primarily malabsorptive operations in relatively small numbers once the initial success by Scopinaro and colleagues was demonstrated for the biliopancreatic diversion (BPD)\(^7\) (Fig. 37-3). Later, to avoid the high rate of marginal ulcer seen after BPD, both Marceau and Hess performed the duodenal switch (DS) (Fig. 37-4), which modified the
gastric portion of the operation and used a duodenoileal anastomosis.\textsuperscript{8,9}

\textbf{FIGURE 37-3} Biliopancreatic diversion.
The advent of performing bariatric surgery laparoscopically evolved in the decade from 1994 to 2004, during which time Wittgrove’s initial success\textsuperscript{10} doing a laparoscopic gastric bypass was reproduced by others including Schauer\textsuperscript{11} and Nguyen.\textsuperscript{12} Gastric bypass was the procedure of choice at the time, and the one that U.S. surgeons learned to do initially laparoscopically. In 2003, the FDA approved the use of the laparoscopic adjustable gastric band (AGB) (Fig. 37-5), which had risen rapidly in popularity in Europe and
Australia since its first performance by Belachew in 1993.\textsuperscript{13} The lap band was technically easy for surgeons to place, and it enjoyed considerable popularity in the United States for the next 5 to 6 years. However, by that time it became clear the long-term results of the band were not what had been expected, and many patients began demanding to have them removed and revised to other procedures. By 2015, the lap band represented only about 5\% of bariatric procedures performed in the United States, and for 2014 the published figure is 7.4\%.\textsuperscript{14}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure37-5.png}
\caption{Adjustable gastric banding.}
\end{figure}

Concurrent with the fall of the lap band was the rise of the sleeve gastrectomy (SG) (Fig. 37-6). It was originally performed as the gastric portion of the DS operation. When the DS was performed laparoscopically, the initial experience by Gagner showed a higher than expected morbidity and mortality.\textsuperscript{15} The operation was then divided into two stages, with the laparoscopic gastric portion of the operation being initially done, after which,
with weight loss, the malabsorptive portion of the operation was added. However, many patients had such good success after just the gastric portion, they would not agree to any further surgery. Their success then stimulated surgeons to perform the SG as a primary procedure. It has now become the most popular procedure done both in the United States and internationally.

**FIGURE 37-6** Sleeve gastrectomy.
The history of bariatric surgery has been intertwined with the history of metabolic surgery. The two have now become relatively synonymous, but it has only been in the past 15 years that there has been significant attention devoted to studying the metabolic effects of bariatric operations. Pories and others had reported the astonishingly fast reversal of type 2 diabetes after gastric bypass many years earlier, but few others had focused on the changes that the operation caused in glucose metabolism until this century. Mechanisms of alterations of glucose metabolism, changes in systemic cytokine production, the variances and effects of the gut flora on metabolism, influences of circulating gastrointestinal hormones and other vasoactive peptides, and the role of neural input to satiety, food intake, and absorption have all been and are being studied currently, yielding a growing body of scientific knowledge to explain the clinical efficacy previously seen but not fully understood that is produced by bariatric operations. Adding to such knowledge in the future can only serve to improve the effectiveness of combatting obesity and its associated significant metabolic and systemic illnesses that serve as the leading cause for the now observed reversal of life expectancy from progressively longer to stable or possibly shorter for the next generation.

THE DISEASE OF OBESITY

The disease of obesity is complex, multifactorial, and cannot be adequately addressed in full detail in this chapter. However, there do seem to be some essential components that are important to the abnormal gain of weight by individuals who suffer from severe obesity. These include

1. An occasional or steady alteration in satiety such that large quantities of food may be ingested in a single sitting
2. Some genetic component to the disease, as yet still not well understood
3. A likely environmental component to the disease, based on eating habits, lifestyle, and activity and exercise levels of individuals
4. New evidence that gut flora may be important in influencing amounts of food absorbed between normal-weight and obese individuals

Obesity is currently classified into several categories. Table 37-1 gives the
current Western definition of the classes of obesity, based on body mass index (BMI) (weight in kg/height in meters squared). Asian countries employ a slightly different classification, with class 1 obesity beginning with a BMI of 27. Severe obesity is associated with numerous comorbid medical problems. They are listed in Table 37-2. The major medical reason for performing metabolic and bariatric surgery is to improve these medical problems. While they are quite clear-cut, and the improvements of them have been well documented in the literature, they are not always the major reason for having surgery from the patient’s point of view. Often the patients are quite concerned with these problems, but they also may suffer from other less medically significant but just as altering lifestyle problems including ability to ambulate without difficulty, ability to bend and reach objects, to dress easily, to buy clothes off the rack, to be able to comfortably fit into seats for air travel, to drive a car comfortably, and to be able to play and interact with children and grandchildren. Loss of positive self-feelings, loss of sexual function and ability, and limited physical abilities to perform activities of daily living or activities required by a job all may play major roles in the patient seeking surgical help for the problem of severe obesity. Resolution of these issues is less well recorded in the literature, but well reflected in the very high patient satisfaction ratings for the results of their metabolic and bariatric operations, even when those operations do not meet the “standard” definitions of success we as surgeons have defined, such as loss of over 50% of excess weight and improvement in medical problems.

<table>
<thead>
<tr>
<th>Class</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>22-27</td>
</tr>
<tr>
<td>Overweight</td>
<td>27-30</td>
</tr>
<tr>
<td>Class 1 obesity</td>
<td>30-35</td>
</tr>
<tr>
<td>Class 2 obesity</td>
<td>35-40</td>
</tr>
<tr>
<td>Class 3 obesity</td>
<td>40-50</td>
</tr>
<tr>
<td>Class 4 obesity</td>
<td>&gt;50</td>
</tr>
<tr>
<td>TABLE 37-2: COMORBID MEDICAL PROBLEMS ASSOCIATED WITH SEVERE OBESITY</td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular
Hypertension
Cardiomyopathy
Increased coronary artery disease
Ventricular hypertrophy and arrhythmias
Right-sided heart failure
Pulmonary hypertension
Cor pulmonale
Increased incidence of VTE
Venous stasis disease

Pulmonary
Obstructive sleep apnea
Asthma

Gastrointestinal
Gastroesophageal reflux disease
Cholelithiasis
Fatty liver disease

Metabolic
Type 2 diabetes mellitus
  Diabetic nephropathy
  Diabetic retinopathy
  Diabetic peripheral neuropathy
Hyperlipidemia
Hypercholesterolemia
Accelerated peripheral vascular disease

Musculoskeletal
Degenerative joint disease
Osteoarthritis
Chronic back pain
Abdominal wall hernias

Neoplastic
Increased incidence of the following neoplasms:
  Breast
  Uterus
  Colon
  Pancreas
  Prostate
Psychosocial issues may also be very prevalent in the background of some patients who develop severe obesity. There is a known higher incidence of being physically, emotionally, or sexually abused as a child. The use of food as a means to combat anxiety, depression, or other adverse emotions may certainly complicate the disease process. Addressing such problems as a comprehensive treatment plan is important for optimal success for many patients. Addictive behavior to a pathologic extent is often felt to be a contraindication to surgery, and addressing such issues preoperatively to determine if the addictive behavior is severe enough to warrant disqualification from surgery is also very important.

NONOPERATIVE THERAPY

The patient who seeks help surgically to combat weight problems and has not tried conservative therapy of dieting, exercise, behavior modification, or other such programs is a true rarity. It is safe to say that virtually all if not all of patients who undergo surgical therapy have tried to diet on their own or under medically supervised plans. Short-term success of loss of 5% to 10% of body weight is not uncommon for such patients, but regain of weight is almost universal and progressive weight gain with advancing age, further pregnancies, or other life crises is the usual history given by patients. The percentage of patients who are successful in losing more than 10% of body weight through diet and exercise programs and keeping it off for years is estimated to be in the 3% range.

PATIENT SELECTION

Selection of patients then, for surgery, is based on the criteria given in Table 37-3. These criteria were established at the time of the last National Institutes of Health (NIH) Consensus conference on surgical treatment of obesity. Most experts agree that the criteria are outdated and need revision. In particular, there is now good evidence in the literature that for stage 1 obesity, surgical intervention can have significant benefits for the treatment of associated medical problems, particularly type 2 diabetes.
TABLE 37-3: INDICATIONS FOR PERFORMING METABOLIC SURGERY

1. BMI \( \geq 40 \text{ kg/m}^2 \)
2. BMI \( \geq 35 \text{ kg}^2 \) and a comorbid medical problem associated with obesity such as type 2 diabetes, hypertension, obstructive sleep apnea, etc.
3. Failed diet attempt
4. Psychologically stable for surgery
5. No significant active addiction problem
6. Motivated and capable of understanding lifestyle changes

The actual criteria from that NIH conference also included the need to follow patients long-term. While all attempts to do so have been exercised by many practices, including our own, a very high follow-up rate is difficult to achieve long-term due to a variety of problems, including but not limited to loss of insurance coverage for follow-up visits, geographic relocation, and simple lack of motivation to take a day off work to be seen when one is doing well and follow-up is already well established with the primary care physician. We recently were able to document the fact that our approximately 20% to 25% follow-up rate for patients based on voluntary return to clinic annually was an excellent representative sample of the outcomes of the whole group. When the group of patients who had been seen in follow-up regularly for over ten years after gastric bypass was compared to those patients who had not been seen recently but were re-contacted through a special study, there was no difference in the outcomes for the group that had been followed closely versus the one that had been lost to follow-up.\(^{23}\) We feel these data debunk the popular criticism raised in the past of many publications reporting results after metabolic and bariatric surgery which did not have a high follow-up percentage of patients. It is likely the patient sample being seen is representative of the group, based on our experience.

Controversial criteria for inclusion of patients for metabolic and bariatric surgery include age, weight (upper limits), and sometimes individual surgeon requirements for adherence to preoperative diets and cessation of any addictive habits. Relative to age, the younger range of patients can be variable. Large series of adolescent patients have been reported after undergoing metabolic and bariatric surgery, with good success.\(^ {24}\) Most
bariatric surgeons who are not pediatric surgeons, however, do not include many patients under the age of 18 in their practice, but there is no hard and fast rule on this. Similarly, some bariatric surgeons have an upper age limit for performing various operations. Others assess patients on an individual basis for likelihood of being able to physiologically tolerate and recover well from surgery. While many series of older patients have been reported with successful outcomes in the literature, careful scrutiny of larger collected databases reveals the invariable increased incidence of postoperative mortality and slight increases in morbidity for the population over age 65.25

Some surgeons impose a mandatory preoperative diet to achieve a small amount of weight loss for their patients. A few have published a demonstrated benefit for doing so, largely to eliminate the potential for a fatty liver and its technical interference with surgery.26 However, insurance companies have almost uniformly now adopted a policy of requiring patients to complete a medically supervised diet. This can be as long as 12 months. The benefit of such preoperative diets has clearly been shown to be negative in the literature, and such onerous requirements often serve only to delay the ability of patients in need of the benefits of surgical therapy to receive them. The American Society for Metabolic and Bariatric Surgery (ASMBS) has recently published a review of this topic with strong recommendations against this practice.27

Many practices and institutions have upper limits of weight at which they will no longer offer metabolic and bariatric surgery. We also have such a limit, though it is high (600 lbs). At very high weights, the ability to safely perform surgery and to diagnose and treat potential postoperative problems becomes prohibitive if the size of the patient precludes postoperative imaging studies, safe transfer and ambulation, and adequate facilities to meet the patient’s needs.

CENTERS OF EXCELLENCE

Most centers that now perform bariatric surgery participate in the Centers of Excellence program under the supervision of the American College of Surgeons (ACS) working together with the ASMBS. The merger of the two systems of accreditation for bariatric surgery centers happened about 6 years ago, and the current Metabolic and Bariatric Surgery Accreditation and
Quality Improvement Program (MBSAQIP) certifies most medical centers in the country that perform metabolic and bariatric surgery. This centers of excellence concept has been instrumental in improving the overall quality of surgical care rendered to patients undergoing metabolic surgery. Standards for professional training, surgical outcomes, patient education and follow-up, use of a multidiscipline team approach, equipment and supplies in both the inpatient and outpatient settings, and reporting of data all are important components to the accreditation formula, which has produced demonstrably better outcomes in centers of excellence versus centers that have not been a part of such a system.²⁸

The benefit of a multidiscipline team in rendering the best possible care for patients is generally espoused by those with experience in the field. The MBSAQIP recognizes the need for such an approach. Table 37-4 gives a list of the essential and the desirable professionals that are best incorporated into the multidiscipline approach to metabolic and bariatric surgery.

**TABLE 37-4: PROFESSIONAL MEMBERS OF THE MULTI-DISCIPLINE TEAM CARING FOR THE PATIENT UNDERGOING METABOLIC AND BARIATRIC SURGERY**

**Essential**
- Surgeon
- Program coordinator
- Nutritionist
- Primary care physician
- Medical specialists as needed for existent diseases

**Highly Desirable**
- Psychiatrist
- Data coordinator
- Office staff experienced in dealing with these patients
- Bariatrician
- Insurance specialist
- Exercise physiologist
PREOPERATIVE EVALUATION AND PREPARATION

Once a patient has decided they wish to undergo metabolic and bariatric surgery, the single biggest hurdle they face in the United States today is obtaining insurance approval for this procedure. Despite many articles in the literature documenting the long-term financial savings in health care costs for patients who undergo metabolic surgery versus those who do not, the current climate of insurance support for these procedures is one of near hostility. Other than an innate bias against obesity and the concern that a loosening of criteria would bring a wave of patients to receive the benefits of appropriate surgery, there seem no other logical explanations other than the fact that the average duration of an insurance policy may only be about as long as the time it takes for the benefits of surgery to be seen long-term in terms of financial savings. Thus if an insurance company is concerned only about that quarter or yearly expenses, they could conceivably take a position that the short-term cost savings are not adequate to support metabolic surgery. However, if all the insurance industry were to adopt the policy of supporting these procedures, then the well-documented savings in costs to patients over a 3-year or longer period would be realized. In the state of Virginia, for example, there is actually a law that states any insurance company that offers comprehensive health insurance must offer treatment for severe obesity, including a surgical option. What the insurance companies have done, however, is make such coverage contingent upon a special rider to the policy that charges an exorbitant amount (for example, $5000 extra per patient per year) for this coverage. Small employers cannot afford these major increases in premiums. Small employers in Virginia have also recently been denied the ability to obtain bariatric coverage for any price if their number of employees is very low. Thus the only patients who are currently able to obtain insurance approval in Virginia at this time are largely employed by the state, large corporations, or have federal insurance (Medicare and Medicaid). These riders have effectively eliminated access to health care for many deserving patients in the state of Virginia. The story is repeated in many versions across the country. Obesity remains the last unlegislated bias in our society.

If a patient is fortunate enough to potentially receive insurance approval
for metabolic and bariatric surgery, the other issues that need to be decided early on are:

1. Appropriateness for surgery as judged by the multidiscipline team
2. The most appropriate procedure for the patient and agreeable to her/him
3. Identifying and optimally preoperatively treating associated comorbid medical problems

Sufficient preoperative visits to determine the answers to all three of the above issues are needed. For our practice, our initial visit encompasses multidiscipline evaluation, extensive teaching, and identification of medical problems. The most appropriate operation is also chosen. A period of time in which insurance company requirements are then fulfilled, insurance approval is obtained, and medical issues are optimally treated then follows. Finally, another clinic visit in which review of the operative procedure, reinforcement of perioperative expected outcomes, review of expected measures to speed safe surgery and recovery, and the early phases of postoperative diet and exercise plans are again reviewed. The operative consent is discussed in great detail. A date for surgery is chosen.

**Choice of Operation**

Patient preference does play a role in choice of operation. If a patient simply will not undergo an operation, that is the end of that discussion. I would prefer to offer a patient some surgical therapy that will treat his or her severe obesity and its medical problems to a great extent, even if it is not the most optimal operation for a patient, than perform nothing. A few exceptions exist of course to this general statement. Some guidelines we use in helping to select operative procedures are as follows:

1. RYGB results in better treatment of preoperative gastroesophageal reflux disease (GERD) and severe, especially insulin-dependent type 2 diabetes.
2. Patients who are smoking are not candidates for RYGB (complications of marginal ulcers).
3. The laparoscopic AGB has a very limited applicability for likely success.
4. Patients with extensive bowel surgery are likely best served with an SG.
Currently, SG has replaced gastric bypass as the most commonly performed procedure in the United States and in the world (Table 37-5). This popularity is likely due to its efficacy to date, and the fact it is a technically easier procedure for the average laparoscopic surgeon to perform. Patients are also demanding it because of the often-verbalized perception that it is “less invasive.” While it does avoid any change in the route of the alimentary tract, sending 70% of the stomach to the pathologist is not exactly less invasive. It does also have the benefit of having less long-term complications, especially avoiding the problems of bowel obstruction and marginal ulcers seen after gastric bypass. For many patients, the SG is very appropriate. We tend to recommend gastric bypass for patients with significant GERD, significant type 2 diabetes, and who have a BMI over 60. Some surgeons would argue the patient with a BMI over 60 should undergo a malabsorptive operation, and that is valid based on the outcomes data. However, I have chosen not to perform malabsorptive procedures since our patient population often comes from a long distance and keeping close follow-up is very difficult. Close follow-up is uniformly felt to be a requirement for performing malabsorptive procedures such as the duodenal switch.

### TABLE 37-5: PERCENTAGES OF METABOLIC AND BARIATRIC OPERATIONS DONE IN THE UNITED STATES 2011-2016

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>158,000</td>
<td>173,000</td>
<td>179,000</td>
<td>193,000</td>
<td>196,000</td>
<td>216,000</td>
</tr>
<tr>
<td>RYGB</td>
<td>36.7%</td>
<td>37.5%</td>
<td>34.2%</td>
<td>26.8%</td>
<td>23.1%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Band</td>
<td>35.4%</td>
<td>20.2%</td>
<td>14%</td>
<td>9.5%</td>
<td>5.7%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Sleeve</td>
<td>17.8%</td>
<td>33%</td>
<td>42.1%</td>
<td>51.7%</td>
<td>53.8%</td>
<td>58.1%</td>
</tr>
<tr>
<td>BPD/DS</td>
<td>0.9%</td>
<td>1%</td>
<td>1%</td>
<td>4%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Revisions</td>
<td>6%</td>
<td>6%</td>
<td>6%</td>
<td>11.5%</td>
<td>13.6%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Other</td>
<td>3.2%</td>
<td>2.3%</td>
<td>2.7%</td>
<td>0.1%</td>
<td>3.2%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Balloons</td>
<td>&lt;0.3%</td>
<td>2.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RYGB, Roux-en-Y gastric bypass; BPD/DS, bilipancreatic diversion with duodenal switch.

### Evaluating Medical Problems

Once the operation has been chosen, the patient must be evaluated and treated for associated comorbid medical problems. The medical problems most often not identified prior to our evaluation have included obstructive sleep apnea, hyperlipidemia, and gallstones. However, the entire list of problems given in
Table 37-2 should be assessed for existence, and tested for if they may be present. Appropriate preoperative treatment is indicated. Baseline metabolic deficiencies that are common in the patient population considering metabolic surgery include iron deficiency anemia, vitamin D deficiency, and hyperglycemia from unrecognized early diabetes. Common preoperative screening tests we employ include an upper endoscopy for anyone with symptoms of GERD. Detection of Barrett esophagus, though infrequent, is essential preoperatively. The incidence of lesions that may alter the surgical treatment to some extent has been approximately 5% based on our historical data.33 A sleep study is ordered for patients with high assessment scores for sleep apnea. An ultrasound of the gallbladder is routinely performed for all patients with a gallbladder. Other pertinent positives in the history and physical include risk factors for increased incidence of venous thromboembolism (VTE), including previous history of VTE, pulmonary hypertension, and venous stasis ulcers.

During this evaluation, conditions that might merit simultaneous second surgical procedures may be identified. The two most common are gallstones and abdominal wall hernias. We have recommended that patients who have gallstones undergo a simultaneous laparoscopic cholecystectomy. Our results in performing this procedure associated with gastric bypass have been published and show an extremely low (less than 1%) incidence of complications from the cholecystectomy as well as no increased length of stay or morbidity.34 For patients who do not have gallstones, we advocate a 6-month course of ursodiol at 300 mg bid to decrease the incidence of postoperative gallstones to approximately 4% (data obtained after gastric bypass).35

Abdominal wall hernias are not infrequent in this patient population. The most common primary one is umbilical hernia. If an umbilical hernia is large enough to potentially have a loop of bowel incarcerate in it postoperatively, it should be repaired. Studies carried out on the question of whether to repair abdominal wall hernia defects at the time of gastric bypass or defer repair until later have shown a significantly high incidence of incarcerated hernias needing emergency surgery when the hernia was not repaired at the time of the gastric bypass.36 Now, even the use of mesh to repair abdominal wall defects after SG has been shown to be safe, based on negative intraoperative peritoneal fluid cultures during one study.37 For the extremely large hernia
where there is significant bowel involvement in the hernia sac, performance of an open procedure to repair the hernia and do the metabolic operation simultaneously seems the best choice. In this patient population, the incidence of postoperative infections is less well documented, so primary repair and closure if possible is still recommended until further data are available.

The most commonly unplanned procedure performed during metabolic and bariatric surgery is a liver biopsy. Some institutions perform them routinely or nearly routinely, so that the procedure is not unplanned. However, most practices, ours included, will perform a laparoscopic liver biopsy based on the gross appearance of the liver. Any excessive fattiness, and certainly any evidence of scarring are indications for a biopsy. Biopsy results showing any degree of fibrosis should have follow-up with a hepatologist.

**Patient Education**

The major components of preoperative preparation are optimal treatment of medical problems, patient education, and adherence to planned preoperative protocols as indicated. We have discussed the treatment of existing medical problems above. The importance of preoperative education and teaching is paramount. Patients who are educated and know what to expect will be much more at ease with the events before and after surgery. They will be prepared to follow instructions and recommendations more closely, with better outcomes. Realistic expectations of time in the hospital, pain and its treatment, expected recovery time, and other postoperative issues should all be well discussed before surgery.

**Preoperative Protocols/ERAS**

Preoperative protocols differ from institution to institution. Many institutions now have adopted the early recovery after surgery (ERAS) type guidelines for many procedures, including metabolic surgery. The truth is, metabolic surgery, by doing virtually all procedures laparoscopically, emphasizing early ambulation as a prophylaxis against VTE, and avoiding nasogastric tubes and introducing liquids soon after surgery, had already achieved many of the
main components of the ERAS protocol. Improvements in pain control and volumes of intravenous fluids given during surgery by our anesthesiology colleagues have been definite benefits of an ERAS program. The ability of patients to take liquids until 2 hours prior to surgery has also been a benefit for our patients, who otherwise were often a bit dehydrated at the start of surgery since their daily liquid requirement is increased due to increased body habitus.

Other than ERAS protocols, some practices have incorporated preoperative diets of the short-term low-carbohydrate variety for their patients. We have not used this approach, and have had few reasons to consider doing it. Enforcement and the penalties for noncompliance seem to be more difficult issues for us than the benefits. Such benefits of a preoperative diet have been reported by some surgeons in surgeon-supervised diets, but the overall improvements in outcomes have been modest and not enough to recommend that this practice be uniformly adopted.²⁷

VTE prophylaxis is important, yet there is no one agreed-upon formula. Based on the clinical practices of members of the ASMBS,³⁹ most patients receive sequential compression foot or leg devices to wear during surgery and while hospitalized postoperatively. Most patients also receive chemoprophylaxis using either regular or low molecular weight heparin. Most surgeons begin this just prior to surgery, with subcutaneous prophylactic doses based on weight. The duration of chemoprophylaxis is controversial. High-risk patients should get a longer course, but whether that is 1 week or up to 4 weeks or longer is still unclear. Despite the importance of this topic, and the fact that pulmonary embolism remains the leading cause of death after metabolic and bariatric surgery, there is still not widespread agreement on the type of heparin, its timing and duration that is optimal for prophylaxis.³⁹

Preoperative antibiotics given intravenously within 1 hour prior to starting surgery and redosed until the procedure is completed (and in some institutions up to 24 hours later) has been proven effective in decreasing surgical skin site infections.

**Postoperative Protocols and Follow-Up**

Postoperative protocols have evolved over the years to now embrace
relatively early discharge from the hospital. Sleeve gastrectomy patients being discharged on the first day after surgery, and gastric bypass patients being discharged either then or the second day after surgery are well published and accepted as safe practice. Early ambulation, early feeding, and minimizing opioid narcotic use with substitution of other non-narcotic pain medications are now hallmarks of most postoperative protocols after metabolic surgery.

Long-term postoperative follow-up has always been advocated to determine the outcomes of the intervention of metabolic and bariatric operations. As noted above, we now have evidence that a substantial sampling, without complete follow-up, of patients probably gives an excellent approximation of the true outcomes of long-term results. Metabolic side effects and consequences exist for all the operations, though the malabsorptive procedures have much greater potential metabolic derangements long-term.

**Nutritional Issues Following Surgery**

Completely restrictive operations that do not alter the alimentary tract, such as the laparoscopic AGB, have the only consequence of decreasing total nutrient intake. A multivitamin is all that is recommended for postoperative prophylaxis. For the SG, where the stomach is decreased in volume, adding a reliably absorbed source of vitamin B₁₂ is indicated due to the role of the stomach in its normal absorption. Patients who undergo gastric bypass are at risk for malabsorption of iron and calcium, both preferentially absorbed in the duodenum and proximal jejunum. Diversion of the stomach from the food stream also decreases B₁₂ absorption. Supplements for these two minerals and vitamin B₁₂ are indicated as well as a multivitamin to protect against low folate levels or other vitamins not as well absorbed after gastric bypass. Malabsorptive operations, such as the duodenal switch, can produce protein calorie malnutrition as the most severe consequence. Parenteral nutrition may be needed to correct malnutrition, and the reoperative rate to address long term consequences is approximately 7%. Periodic replacement of fat-soluble vitamins via a parenteral route in addition to all the supplements recommended for gastric bypass is standard for patients after a duodenal switch. For all patients who have metabolic surgery, annual or more frequent
follow-up by a physician (primary care or surgeon) is indicated long-term to help monitor and prevent any of the above vitamin and mineral deficiencies.

THE OPERATIVE PROCEDURES

In 2017, there are now two main operative procedures done as metabolic and bariatric operations: SG and RYGB. There are two procedures uncommonly done: laparoscopic AGB and DS. There is also an emerging, not yet considered standard procedure gaining popularity that may well become a standard procedure in the near future: single anastomosis gastric bypass (SAGB). Finally, there are nonsurgical weight loss options now available for patients with class 1 obesity such as intragastric balloons, endoscopic sleeve gastroplasty, and others, which are described below as well. Operative procedures that have only historic interest, such as vertical banded gastroplasty or biliopancreatic diversion are not described, as they are now rarely performed. A special section on revisional operations is also included. In addition, no longer is any extensive description given to open operative procedures, as they have now all been well eclipsed by their laparoscopic counterparts and have relevance only in a historic sense or in operative procedures where previous surgical scarring (such as in revisional surgery) make an open approach necessary. In general, few variations from the laparoscopic approach in terms of the operative steps are needed when converting from laparoscopic to open surgery. Thus all operative descriptions to follow assume a laparoscopic approach is used. The operative descriptions below are how I perform these operations. Most can have significant variability in the steps and techniques and still accomplish the same operation, and this is certainly acknowledged.

Sleeve Gastrectomy

TECHNIQUE

Port placement involves a 12-mm camera port approximately 15 cm down from the xyphoid and just to the left of the midline, two ports for the surgeon in the right upper quadrant, with the lower of the two being a 15-mm port and the upper a 5 mm port. The operation is best conducted if the skilled first assistant has two 5-mm ports in the left upper quadrant for assisting. (Fig. 37-
We also favor always using a 10-mm 45-degree telescope for our procedures.

FIGURE 37-7 Port positions for lap sleeve gastrectomy.

The liver is retracted with a Nathanson retractor, placed in the left xyphoid region to retract the left lobe of the liver. The pylorus is identified. The harmonic scalpel is used to divide the attachments to the greater curvature of
the stomach beginning 4 cm proximal to the pylorus and ending at the left crus of the diaphragm (Fig. 37-8). Care must be taken to avoid splenic injury in dividing the short gastric vessels. Any posterior gastric adhesions should also be divided so that the stomach is mobilized on the lesser curvature blood supply and the prepyloric vessels.

The sleeve is now created. Using an intragastric dilator or tube is helpful to gauge sleeve luminal size. It has been shown that a 40 Fr dilator is optimal size for the lumen. Anything smaller must not be directly touching the stapler as it is closed, or too narrow a lumen may result. The area where narrowing is most common and is most concerning is the incisura. Staple height is gauged by stomach thickness, with higher staple height loads being used on the antrum and shorter ones on the fundus. Controversy exists as to whether to use buttress material while stapling. Large pooled data show a slight difference in favor of less bleeding if such buttressing is used, but the differences are not appreciable in common practice. Leaks are no different whether buttressing is used or not. Some surgeons reinforce their staple lines with oversewing, and some suture only areas of obvious bleeding or concern.

I personally use an Ewald tube (34 Fr) and place the stapler close but not directly adjacent to it while it is positioned along the lesser curvature (Fig.
37-9). Once the sleeve is created, the tube serves as a good mechanism for injecting methylene blue dye forcefully into the stomach to confirm security of the staple line. The resected stomach is removed through the 15-mm port site, enlarging it slightly as needed. We close all port sites 10 mm or larger with interrupted suture or sutures of 0 Vicryl placed laparoscopically with a Berci suture passer.

FIGURE 37-9  Stapling the stomach to create the sleeve.

OUTCOMES

SG has been shown to produce an excess weight loss at 8 years of 67% in one series.\textsuperscript{41} It improves medical conditions quite well, as shown in data from the ACS Bariatric Surgery Center Network (BSCN) initial report on the first 900 plus such procedures recorded in that database\textsuperscript{42} (Table 37-6). The one medical problem that is not well treated by SG is GERD. Patients who have GERD have been shown to do less well on the whole than those who do not. GERD is reported as variably improved after SG. In the ACS database, it was improved in 50% of patients versus 70% after RYGB.\textsuperscript{42} In other series GERD was reported to arise anew in from 8% to 47% of patients previously asymptomatic after SG.\textsuperscript{43,44} Preoperative and intraoperative search for the presence of a sliding hiatal hernia, and its subsequent repair at the time of SG
can improve these results. Barrett esophagus is considered a contraindication for SG by many surgeons.

### TABLE 37-6: DATA ON IMPROVEMENT IN COMORBID MEDICAL CONDITIONS FROM ACS BSCN CENTERS BY OPERATIVE PROCEDURE

<table>
<thead>
<tr>
<th>Condition</th>
<th>LAGB</th>
<th>LSG</th>
<th>LRYGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>44</td>
<td>55</td>
<td>83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>38</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>33</td>
<td>35</td>
<td>66</td>
</tr>
<tr>
<td>GERD</td>
<td>64</td>
<td>50</td>
<td>70</td>
</tr>
</tbody>
</table>


Thirty-day mortality for SG has been at approximately 0.1% to 0.25% nationally and internationally in large series.\(^{42,45}\) Early severe postoperative complications have been in the 4% to 5% range, including leak rate of approximately 2.4%, bleeding rate of also approximately 1%, and stenosis rate of approximately 2.1% that needed reintervention.\(^{46}\) Overall postoperative complication rates are given as approximately 9% for SG.\(^{42}\) We have observed an approximately 6% incidence of excessive nausea unexplained by any anatomic finding postoperatively. These patients have a syndrome similar to morning sickness, and anti-emetics, intermittent intravenous fluids, and supportive encouragement allow them to weather the usually 1- to 2-month duration of symptoms. Fortunately, the long-term complication rates for this operation, as witnessed in our own practice, are limited to weight regain and a few rare cases of late stenosis and exacerbation of GERD.

**TREATING COMPLICATIONS**
Early recognition is always important in treating complications. Isolated tachycardia or dyspnea can be the only early sign of a staple line leak. Waiting until the patient is febrile, has peritonitis and hypotension, leukocytosis on labs, and a radiograph showing a leak before instituting treatment puts the patient at risk for mortality. A high index of suspicion must be present when dealing with suspected leaks. The clinical picture, not just a radiographic study, should determine reoperation. Leaks most commonly occur in the proximal staple line, as a result of high pressure generated by stenosis distally in the sleeve. The combination of stenosis and leak presents two issues that must be resolved before the patient can be functional. Late leaks (over 7 days after surgery) do occasionally present after SG, whereas they are almost unknown that late after RYGB. Many leaks will present after the patient has been discharged, so this must be considered. The optimal treatment for a leak may vary based on its size and severity. A small leak demonstrated on gastrograffin swallow might on rare occasions be adequately treated with endoscopic suturing and stenting and IV antibiotics. A percutaneous drain may also be needed. Most commonly, however, reoperation involves attempting to close the leak if feasible with sutures, placing multiple drains, and creating a jejunostomy tube for enteral feeding access. Leaks after SG can be notoriously difficult to resolve. They tend to not heal quickly, and may become chronic. If so, endoscopic stenting early after surgery may help if the anatomy of the leak area is favorable to a stent. Long-term leaks (of multiple months’ duration) may require operative conversion to a RYGB at the site of the leak.

Postoperative bleeding is most commonly from the staple line, and bleeding goes largely into the peritoneal cavity. A drop in hemoglobin or hematocrit postoperatively must be followed up to be certain there is no ongoing bleeding. Transfusion and operative therapy are added based on the severity of the bleeding. Operative therapy with suturing of the bleeding is much preferred to radiologic or endoscopic intervention in the immediate postoperative period unless the bleeding is manifested as hematemesis, in which case upper endoscopy is the procedure of choice.

Stenosis is often slightly slower to manifest itself. It may be present acutely after surgery or present within the first 2 months. Confirmation of stenosis by gastrograffin swallow can be followed by endoscopy, which may at times be therapeutic if the stenosis is largely from the stomach twisting and creating a stenotic area at the twist. Retwisting, however, will require
operative intervention to secure the stomach in an untwisted configuration. Most often there is stenosis at the incisura, where the stomach makes its turn. Dilating this endoscopically using pneumatic dilation or fluoroscopically may produce satisfactory results in about half of cases. Stenting further increases the success to an estimated 90% by some reports. Persistent stenosis may require conversion to a RYGB above the site of the stenosis in 10% to 45% of cases.47,48

**Roux-en-Y Gastric Bypass**

**TECHNIQUE**

The RYGB is performed in a variety of ways. The essential elements of the operation are to:

1. Create a small proximal gastric pouch based on the lesser curvature
2. Create a Roux limb of 75 cm to over 150 cm and create an enteroenterostomy at that length to the biliopancreatic limb
3. Anastomose the proximal end of the Roux limb to the proximal gastric pouch

Variations of the operation include the route of the Roux limb (retrogastric retrocolic to antegastric antecolic and all variations), the length of the Roux limb, and the means of creating the gastrojejunostomy (linear stapling, circular stapling, and hand suturing). Closure of mesenteric defects is done by most but not all surgeons. Testing the gastrojejunostomy for leaks is done by most but not all surgeons.

My personal technique is as follows:

Ports are placed in a similar location for SG (see Fig. 37-7), but the camera port is placed a few cm lower, and the surgeon’s right-hand and the assistant’s right-hand ports are 12-mm ports to accommodate the stapler. The omentum is elevated, and the ligament of Treitz identified with certainty. The proximal jejunum is divided 40 to 50 cm distal to the ligament of Treitz with a linear stapler (Fig. 37-10). The mesentery at that site is then further divided toward its base to maximally mobilize the Roux limb. Division is stopped short of encountering the base of the mesentery with its large vessels. The proximal end of the Roux limb has a small Penrose drain sutured to it for
identification and manipulation. The desired length of the Roux limb is then measured out, placing the proximal Roux limb into the left upper quadrant as this measurement occurs. The location on the jejunum for the enteroenterostomy is lined up adjacent to the proximal jejunum, with both lengths of bowel lined up in an isoperistaltic fashion so the mesentery is flat adjacent to each other (avoid twisting the distal jejunum so that it is antiperistaltic). The enteroenterostomy is created using a double fire staple technique with the linear stapler (Fig. 37-11). The stapler defect is sutured closed. The mesenteric defect is then sutured closed.

FIGURE 37-10 Dividing the jejunum to create the Roux limb of RYGB.
The transverse colon mesentery is exposed in the area of the ligament of Treitz. A defect is made in the mesentery a few cm to the patient’s left and just above the ligament. This placement usually allows for creation of a defect in the mesentery that avoids major vessels and allows a large enough opening to be created to see the posterior stomach. The stomach is grasped and pulled into the opening, after which the Penrose drain and the proximal 2 inches of the Roux limb are placed into the retrogastric space (Fig. 37-12). Care must be taken to be certain that the Roux limb mesentery is not twisted.
FIGURE 37-12  Placing the proximal Roux limb behind the stomach in a retrocolic retrogastric position.

The Nathanson liver retractor is placed in the left xyphoid area and the left lobe of the liver retracted. The harmonic scalpel is used to make an opening adjacent to the lesser curvature of the stomach, just above the incisura. For especially large patients, this opening should be made more distally, at the incisura, to insure enough length of the proximal gastric pouch to reach the Roux limb without tension. A green load of the linear stapler is used to partially divide the stomach from the lesser curvature side (Fig. 37-13). The surgeon must be certain all tubes are removed from the stomach before firing. Then an Ewald tube is placed into the gastric lumen by the anesthesiologist, and lined up along the lesser curvature of the stomach. It is used as a guide against which are placed subsequent loads of the linear stapler to divide the proximal stomach and finish creating the proximal gastric pouch (Fig. 37-14). Once that pouch is created, the Penrose drain is located in the retrogastric region and used to bring the Roux limb up such that the staple line is facing directly toward the camera. The proximal Roux limb is then sutured to the distal gastric pouch so the two are side by side. Then a gastrojejunostomy is created using a blue load of the linear stapler, fired to its full length (Fig. 37-15). The stapler defect is sutured closed, reinforced with a second suture line,
and tested for integrity by forcefully infecting methylene blue into the anastomotic area via the Ewald tube (which was withdrawn several inches at the time of stapling of the gastrojejunostomy and subsequently repositioned at the anastomosis). Sutures are placed in the transverse colon mesentery and between the Roux limb and biliopancreatic limb to close mesenteric defects (Fig. 37-16).

**FIGURE 37-13** Dividing the stomach partially from the lesser curvature to begin creating the proximal gastric pouch.
FIGURE 37-14 Completing division of the stomach to create the proximal gastric pouch.

FIGURE 37-15 Creating the gastrojejunostomy (linear stapled technique).
FIGURE 37-16 Closing the mesenteric defects for retrocolic retrogastric RYGB.

OUTCOMES

The RYGB has been shown to produce, in general, approximately 65% to 75% excess weight loss at 1 year. We have shown the 10-year weight curve stabilizes at approximately 50% of excess weight loss.\(^4^9\) Weight regain tends to be not uniform: many patients maintain all their weight loss, while about 30% experience considerable weight regain. Resolution of comorbid medical problems remains true even after 10 years, as shown in Table 37-7.\(^4^9\) RYGB has been especially effective in treating insulin-dependent type 2 diabetes.\(^5^0\) It also is far superior to SG in treating GERD.\(^5^1\) We have shown it is also an effective operation for patients with a BMI over 60.\(^5^2\)

TABLE 37-7: DATA ON RESOLUTION OF COMORBID MEDICAL PROBLEMS 10 YEARS AFTER GASTRIC BYPASS FROM OUR UVA SERIES
Mortality for laparoscopic RYGB published from the ACS database shows a 0.15% 30-day mortality.\textsuperscript{42} Other databases confirm this extraordinarily low number, with the Bariatric Outcomes Longitudinal Database figure being 0.12%.\textsuperscript{53} It is especially gratifying to see these results since only a little more than a decade earlier, data were published from the decade previous to that showing a 2% mortality in patients with federal insurance after RYGB.\textsuperscript{54} Many of those patients, however, had their operations performed open before the age of laparoscopy. Nevertheless, a documented greater than tenfold decrease in mortality for an operation in a 15- to 20-year period is most remarkable, and is probably not duplicated in the surgical literature for another procedure.

Complication rates for laparoscopic RYGB from the ACS BSCN database showed a 14% 30-day postoperative complication rate, with a reoperative rate of 5%.\textsuperscript{42} Leaks after RYGB have been consistently in the 1% range.\textsuperscript{55} Bleeding is in the 1% range as well.\textsuperscript{56} VTE is reported in just under 1% of cases, and pulmonary embolism remains a leading cause of death.\textsuperscript{53} Longer term complication rates after RYGB include a marginal ulcer rate reported as widely varying between 2% to 12%, which may reflect the degree of aggressiveness and classification of the reporting authors or the surgical techniques used.\textsuperscript{57} Small bowel obstruction is generally given as about 5% now, since the majority of surgeons have adopted closing mesenteric defects. Still, about half of those obstructions are from herniation through mesenteric defects and can represent potential for significant bowel ischemia if not treated promptly.\textsuperscript{58}

### TREATING COMPLICATIONS

As with SG, leaks after RYGB are notorious for often presenting with fairly subtle clinical findings, such as isolated tachycardia or dyspnea. A high index...
of suspicion for the postop patient that “just does not look right” should include leak as the primary diagnosis. The leak may not be manifested on a gastrograffin swallow, especially if it is from the distal gastric staple line or distal anastomosis. A low threshold for reoperation should exist. Operative intervention includes identifying and closing the leak if feasible, placing multiple drains, and for all proximal gastric leaks, placement of a distal gastric feeding tube for enteral nutrition. Enteroenterostomy leaks require repair if feasible, drains, and a more distal jejunostomy tube.

Bleeding after RYGB manifests itself in two ways. Early hematemesis requires return to the operating room and general anesthesia with endoscopic treatment of the bleeding, which is invariably at the anastomosis of the gastrojejunostomy. A fall in hematocrit with or without melena is treated with transfusion and surgery or radiologic intervention if bleeding does not stop after modest transfusion or becomes hemodynamically significant. Radiologic imaging can be very helpful in determining the bleeding site, and may also be therapeutic. If embolized, the bowel usually should be operatively visualized for viability within the next 24 hours.

Acute upper abdominal pain and bloating within a few days after RYGB is a potential life-threatening problem. If there is an obstruction at the enteroenterostomy (alternatively postop hematoma and bleeding could be a cause as could distal bowel obstruction from a port site or abdominal wall hernia) then the distal stomach and its secretions, as well as bile and pancreatic juice, are all trapped in the obstructed lumen, potentially resulting in the rupture of the distal stomach staple line (Fig. 37-17). Such an event is often fatal. Awareness of this problem for any patient with acute pain and pressure in the left upper quadrant within the first few days after RYGB is essential to its timely diagnosis and successful treatment. In general, any vomiting soon after a RYGB is a concern for great worry and the burden of proof is on the surgeon to confirm there is no obstruction.
Later postoperative bowel obstruction can also be life-threatening if it involves the bowel incarcerating in a mesenteric defect. Many patients have lost a significant length of small bowel in this situation, where recognition and treatment of the problem was too late to prevent bowel gangrene.\textsuperscript{60} Once again, the rule of thumb for patients after RYGB is that all bowel obstructions are to be treated operatively unless there is convincing evidence this is a partial bowel obstruction only from adhesions. The operative treatment of a bowel obstruction from a mesenteric defect is to identify the terminal ileum and work retrograde up the ileum to the enteroenterostomy so that there is definitive identification of all parts of the bowel (distal, Roux limb, biliopancreatic limb).

Marginal ulcers can be a very burdensome problem for those patients susceptible to them. The etiology of marginal ulcers is unknown. The hallmark of a marginal ulcer is persistent epigastric pain not responsive to food. Vomiting may occur if the ulcer is acute or chronic, with stenosis of the
gastrojejunostomy. Endoscopy is the best procedure to both diagnose and potentially treat the problem. Endoscopic dilation may be helpful in alleviating obstructive symptoms until the ulcer heals. Most ulcers will heal given appropriate medical therapy. Patients who are smokers have a much lower chance of the ulcer healing while they still smoke. An untreated persistent marginal ulcer can perforate and create a surgical emergency. It can also fistulize into the lower stomach, creating a channel for persistent acid washing back on the ulcer and precluding healing in most situations. Such a gastrogastric fistula usually needs operative treatment. Revision of the anastomosis is needed as well as separation from the distal stomach (and wedge resection). Multiple recurrent ulcers or a gastrogastric fistula in a patient who is a persistent smoker is a situation where takedown of the Roux limb and creation of a gastrogastrostomy may be indicated.

Nutritional consequences of RYGB are not uncommon. Due to the poor absorption of iron, patients will need iron supplementation. An iron form that does not require an acid environment for breakdown and absorption (ie, not ferrous sulfate) is indicated as oral supplementation. The incidence of iron transfusion parenterally in patients after RYGB is appreciable: 8.5% needing transfusion and 58% being anemic in one recent study. Vitamin $\text{B}_{12}$ and calcium, though also not as well absorbed, usually are still adequately absorbed to prevent severe complications from their deficiency. Although the operation has been performed for nearly 50 years, it is still not certain to what degree the potential malabsorption of calcium in patients undergoing gastric bypass produces a major clinical risk for osteoporosis and bone disease. Some literature has documented the increased potential for this, but in practice the number of patients who present with severe osteoporosis after gastric bypass is small. Supplementation of calcium, however, is generally recommended to prevent this problem. Vitamin D is often deficient in the general population, and whether there is a significantly increased incidence of its deficiency in patients who have undergone gastric bypass is not clear or proven. However, when one monitors the vitamin levels of patients who undergo gastric bypass for abnormalities, vitamin D deficiency will be a prevalent problem and require supplementation in a significant percentage of patients, reported in one study in a northern climate as being 64%.

**Laparoscopic Adjustable Gastric Banding**
TECHNIQUE

Port placement for the laparoscopic adjustable gastric banding (lap band) procedure varies from surgeon to surgeon but most often includes placement of a 12-mm port approximately 15 cm below the xyphoid for the camera, and adding a 15-mm port in the lower part of the right upper quadrant and a 5-mm port in the midportion of the right upper quadrant. The assistant then uses either one or two 5-mm ports in the left upper quadrant. A liver retractor is needed. We place a Nathanson retractor in the left epigastric region, similarly to both SG and gastric bypass (Fig. 37-18).

![Port placement for laparoscopic adjustable gastric banding (AGB).](image)

The gastrohepatic ligament is opened in its avascular portion in the area of the upper stomach. This allows visualization of the base of the right crus. The tissue along the base of the right crus is incised and a tunnel developed along the surface of the crura, exiting at the angle of His (Fig. 37-19). A grasper passed through this tunnel then grasps the tubing end of the lap band appliance, pulling it through the tunnel such that the buckle end of the appliance is left anteriorly while the remainder of the lap band and tubing has
been pulled through and around the proximal stomach (Fig. 37-20). The tubing is inserted into the buckle, and the buckle secures the lap band closed. The buckle is positioned along the lesser curvature of the very proximal stomach, about 1 to 1.5 cm below the level of the esophagogastric junction. The fundus of the stomach is then imbricated up over the band in all areas anteriorly except the buckle, with two or three sutures used to imbricate the fundus loosely over the band (Fig. 37-21). The tubing is then brought out through the abdominal wall, with this wound serving as the location of the port, which is connected to the tubing at that site and sutured to the abdominal wall fascia to secure it in place. One type of port had metal claws that secured the port to the fascia. Our preference for port location is in the epigastric region, which allows better palpation and therefore access for postoperative adjustments.

FIGURE 37-19 Creating the tunnel for the lap band against the crura.
FIGURE 37-20 Pulling the lap band appliance through the tunnel prior to securing the buckle closed.

FIGURE 37-21 Imbricating the fundus up over the band to secure it in
Adjustment of the lap band is key to its success. Incremental additions of saline are added to the system through the port via a percutaneous technique. A Huber type needle is necessary to safely access the system. Once the patient’s band has been tightened to the appropriate level, follow-up is less frequently needed from the surgeon, while follow-up with the nutritionist is usually still appropriate on a regular basis.

OUTCOMES

The lap band enjoyed singular success worldwide for about 15 years, from its introduction in 2004 to its high watermark in terms of popularity in the United States in 2009. Since then, it has rapidly fallen out of favor, with more and more surgeons not performing it or performing it on a very limited basis. This is due to the relatively high incidence of poor weight loss long-term in patients who had a lap band placed. Initial weight loss is usually the case with the procedure, but often it is not long-lasting. Regain of weight, though often not rapid, may occur slowly. Also, patients who experienced slippage or prolapse of the band usually had to have all the fluid removed from the system. If the prolapse resolved with that maneuver, additional visits to refill the system slowly back to a restrictive level were needed. Weight regain often occurred if these were not done promptly. Should such scenarios become repeated, the patient would usually become discouraged and asked to have the band removed. Loss of insurance coverage for follow-up visits or any complications of the band also led some patients to seek band removal. In many cases they also then wished to have an alternate procedure done at the time of band removal. Revisional surgery has dramatically increased in the past decade, in large part due to lap band patients having their procedure converted to another one, such as a SG or a gastric bypass.

Initially, the lap band had a good weight loss profile for a medium-term follow-up, with groups reporting an approximately 50% excess weight loss after 2 years, maintained at close to that level for several years. The weight loss curves of lap band patients and gastric bypass patients looked, in some studies, to be on a pattern of representing similar weight loss after about 5 years. However, more problems began to occur with more regularity long-term. Port problems, prolapse, and other issues caused an appreciable
incidence of reoperation. Many patients who had changes in employers in the United States and had a lap band, lost their insurance coverage for subsequent adjustments and therefore stopped the careful follow-up and support and counseling sessions that were shown to be important in the success of the lap band.

Recent studies have shown that the removal of lap bands has occurred in as many as half the patients in some practices in the United States. The incidence of performance of lap band has dropped to under 5% of metabolic and bariatric operations by most recent estimates. In our current practice, the procedure is offered on a limited basis to individuals who have a BMI not much above 40, need to lose only about 75 pounds for health reasons, and are established as being physically active and used to exercising. In such situations, the lap band can be very effective. While it can be effective in other patient demographic groups, the percentage of success is less in our experience.

When patients are adherent to diet and exercise plans and the band is successful, they experience the same resolution of medical problems as with other operations. The lap band was the first procedure to be shown to be effective in treating type 2 diabetes in patients with class 1 obesity. Improvement in hypertension, sleep apnea, hyperlipidemia, and other medical problems is well documented after performance of a lap band procedure.

**TREATING COMPLICATIONS**

Prolapse, or slippage, is the most frequent severe complication that results from the lap band procedure. This occurs when the stomach below the band is pushed up into the center of the band, or conversely the band slips down the stomach such that herniation of a portion of the stomach up through the center of the band occurs. Both descriptors essentially lead to the same problem: too much stomach through the center of the band and situated above it. If the prolapse is severe, the stomach herniated through the band can become so tight that edema cuts off blood flow to the prolapsed stomach and gangrenous changes may result. This situation is life-threatening, and patients present in severe pain and then extremis. Mild cases of prolapse present with more insidious symptoms of increasing obstruction or new-onset GERD. Such symptoms should alert the surgeon to the potential of prolapse. Mild cases of prolapse are easily treated by removing all the fluid within the
system, decompressing the band, and allowing the prolapsed stomach to spontaneously reduce. Patients clinically report immediate relief of symptoms, and can tolerate liquids. If there is any question as to whether prolapse has resolved, an upper GI series is indicated. A plain film of the abdomen may be diagnostic for prolapse as well, with the angle of the lap band changing from a 7 o’clock to a 1 o’clock orientation (just tilted right of vertical) to instead a flat horizontal orientation caused by the prolapse (Fig. 37-22). Failure to reduce the prolapse with removal of all the fluid from the system is an indication for emergent reoperation to revise the band and reposition it (or remove it if the patient requests). Removal is indicated when gastric resection for gangrene has occurred.

FIGURE 37-22 Prolapse of lap band can cause orientation of the band to shift toward a horizontal position.

Port malposition is an unfortunately not uncommon problem. The port, if not properly secured to the fascia, may turn and become oriented sideward or even flip over completely in the subcutaneous space. Proper securing to the anterior fascia of the abdominal wall is the best prevention of this problem. Reoperation may be the only option if percutaneous access ability is lost by
port malposition.

Chronic overfilling of the band system and resulting near-complete gastric outlet obstruction may have the benefit of producing more weight loss but has the negative side effect of causing chronic esophageal dilation above the obstruction point. Left untreated, this can lead to deterioration in esophageal motor function.

Erosion of the lap band may occur as well. In our experience, the few cases we observed were within the first week or two after surgery. Signs and symptoms of a perforated viscus are present. The diagnosis is confirmed by radiographic studies. More chronic erosion of the band may occur as well, but also in low numbers of less than 2% of cases. Port infection, epigastric pain, and upper GI bleeding are all ways in which a chronic erosion may occur. Endoscopic removal of a well-eroded band may be feasible. More commonly, operative removal is needed.

**Duodenal Switch**

**TECHNIQUE**

Port position for laparoscopic DS usually involves two ports in the right upper quadrant, two in the left upper to mid abdomen, and a port near the umbilicus. Additional ports may be added as needed for either of the anastomoses. The operation begins with the creation of a SG. The performance of this is identical to that described above for that procedure. Once the SG has been created, the first part of the duodenum is gently dissected on its inferior border. An area about 2 to 3 cm distal to the pylorus is chosen, and a tunnel is made under the duodenum at that location. The duodenum is then divided with a linear stapler.

The terminal ileum is identified, and an approximately 200 cm length of terminal ileum measured. At that point, the ileum is divided with a stapler, and the distal end of the bowel is brought up to the divided proximal end of the duodenum. There an end-to-side anastomosis is created, usually by suturing, but stapling is also described. The final step of the operation is to create an enterointerostomy between the distal remaining end of the ileum and a position along the terminal ileum usually 100 to 150 cm proximal to the ileocecal valve. The mesenteric defect at the intestinal anastomosis is closed. The resulting anatomy is shown in Figure 37-4.
OUTCOMES

The DS produces the best long-term weight loss of any of the currently recognized conventional metabolic and bariatric procedures. Series have consistently shown 1- to 5-year weight loss of over 66% to 73% of excess body weight. It also appears to have the lowest incidence of failure due to weight regain.

Resolution of comorbidities is excellent with the DS. It is the most effective procedure for eliminating hyperlipidemias of any etiology, as well as being as good as or better than gastric bypass for reversing type 2 diabetes and fatty liver disease. It is also effective against sleep apnea, hypertension, and most other comorbidities associated with obesity. Less has been published on the effectiveness against these latter diseases than has been for gastric bypass, but it is generally felt the improvements would be comparable if not superior. GERD, however, is not treated as well as with gastric bypass, and the DS produces the exact same effectiveness against it as does the SG. Of course this is not surprising given the gastric anatomy of the two operations is identical.

The DS is championed by its advocates as being the optimal metabolic procedure to treat the disease of obesity, as it allows normal gastric emptying via the pylorus, is immune to marginal ulcers, and provides the same effectiveness in terms of reversing the insulin resistance and improving carbohydrate metabolism as that seen after gastric bypass. Since its malabsorptive component serves to limit weight regain, the DS is often considered as the treatment of choice for anyone who has failed a SG or gastric bypass.

TREATING COMPLICATIONS

DS has the potential to have many of the same complications that are seen after RYGB or SG. Gastric staple line leaks, stenosis of the gastric lumen, and bleeding from the staple line are seen in a similar complication rate as SG. Anastomotic leak from the duodenoileostomy or the ileoileostomy may occur in approximately 1% to 3% and 1%, respectively. Stenosis of either anastomosis early after the procedure can present with abdominal pain, distention, and if allowed to progress, blowout of a proximal staple line from obstruction. Signs of distention, pain, vomiting, or any obstructive symptoms
early are cause for immediate determination that no such potentially lethal obstruction exists. The treatment is operative if any doubt exists as to such a condition being present, just as with RYGB.

Late bowel obstruction may occur from an internal hernia. A high index of suspicion must exist to make an early diagnosis. Obstructive symptoms after DS warrant investigation including CT with oral contrast to determine if an obstruction is present. Evidence suggesting a hernia mandates operative intervention to avoid potential bowel necrosis from incarceration through a mesenteric defect.

The other major types of postoperative complications that arise after DS are related to malabsorption and nutrition. Mechanical issues from frequent bowel movements postoperatively can include development of hemorrhoids or perianal excoriation from diarrhea. The treatment is local and alterations in diet to include gut-slowing medications, fiber, and local care. These complications will slow eating if overeating is the etiology. The DS causes malabsorption of a variety of nutrients. Vitamin $\text{B}_{12}$ will be poorly absorbed from the combination of decreased gastric intrinsic factor and decreased terminal ileal absorption of this vitamin. All fat-soluble vitamins will similarly be poorly absorbed due to the decreased exposure to the terminal ileum. Iron and calcium will be very poorly absorbed due to diversion of the food from the duodenum and proximal jejunum, their primary sites for absorption. Thus for DS patients, daily supplementation of iron, calcium, and $\text{B}$ complex vitamins orally is standard treatment. In addition, parenteral administration of $\text{B}_{12}$, fat-soluble vitamins, and at times also iron is also indicated. Nutritional complications seen after DS or other malabsorptive operations are listed in Table 37-8. The relative incidence of such complications in the literature has varied, but just abnormal laboratory values of fat-soluble vitamins after DS was over 60% in some reports.$^{76}$
Protein-calorie malnutrition
Electrolyte abnormalities (especially magnesium)
Fat soluble vitamin deficiencies
Iron deficiency
Calcium malabsorption leading to secondary hyperparathyroidism and bone loss
Vitamin D deficiency
Vitamin B₁₂ deficiency
Folate deficiency
Thiamin deficiency (after any procedure causing vomiting)
Less common documented by may occur:
  Copper deficiency
  Zinc deficiency

Of the minerals that may be inadequately absorbed in patients with malabsorptive anatomy, magnesium is the leading candidate to produce symptomatic malabsorption. Patients may need intravenous magnesium supplementation on a regular basis, but otherwise do not need other parenteral replacement in as frequent a fashion.

Gallstones are almost inevitable after DS if the patient has not had a cholecystectomy. Decreased absorption of bile salts occurs after DS, leading to a decreased bile salt pool and hence a much increased risk of forming gallstones. It is recommended that prophylactic cholecystectomy be considered by many experts who are experienced in performing DS. If cholecystectomy is not done at the index operation, the potential for gallstone formation and its presenting symptoms must be considered when DS patients present with epigastric or right upper quadrant pain years after surgery.

The most concerning nutritional complication that occurs after DS and other metabolic malabsorptive procedures is protein-calorie malnutrition. Hypoalbuminemia after a DS is a concern. The typical symptoms of inadequate protein intake including edema, hair loss, muscle wasting, and even ascites can result. If left untreated, the progressive malnutrition that follows leads to an immunocompromised state and often death from infectious problems as in any malnourished patient. When hypoalbuminemia and symptoms of protein-calorie malnutrition arise after DS, the initial treatment is total parenteral nutrition to correct the problem. If the problem returns or persists, operative revision of the DS to lengthen the “common
channel” of bowel in which the bile and food mix together is needed. No exact formula is known, but most surgeons when faced with this situation will err on the side of providing a significantly longer common channel. The estimated incidence of reoperation for protein-calorie malnutrition varies from 3% to 7% in large reported series of DS.40,77

**Single Anastomosis Gastric Bypass**

Although it has not been officially adopted by the ASMBS as a conventional operation for metabolic and bariatric surgery, the SAGB is developing popularity in other countries and is gaining further converts in the United States. This operation was first introduced by Rutledge and labeled the “mini gastric bypass.”78 Published results showed excellent postoperative weight loss and a complication rate lower than or comparable to the best series of RYGB. However, local reports of a higher incidence of severe bile reflux esophagitis in this patient population than was reported in the literature caused the community of bariatric surgeons to be skeptical of the procedure.79 It has subsequently taken many years and multiple further publications in the literature80-82 to be more accepted internationally and now being considered for adoption in the United States. Since such adoption may occur in the near future, it was felt that at least a brief overview of the procedure is indicated here.

**OPERATIVE TECHNIQUE**

The operation is set up similarly to RYGB. Ports are comparably placed. The operation begins with creation of a proximal gastric pouch much as one would during RYGB. However, the pouch must be started at the incisura to provide an adequately long gastric pouch to limit the potential for bile reflux back to the esophagus. The pouch is made using a dilator or tube as a guide, keeping it narrow as with RYGB, and totally separating it from the distal stomach.

Once the pouch is made, the ligament of Treitz is identified and then a point is chosen from usually 150 cm to 200 cm distal to the ligament of Treitz for creation of the gastrojejunostomy. The anastomosis is normally sutured but can be stapled.
OUTCOMES

Multiple studies have been published in the literature regarding the outcomes after SAGB. Prospective studies initially comparing it to RYGB showed comparable outcomes for weight loss or improved weight loss,\textsuperscript{80} with comparable rates of postoperative complications. Subsequent series have continued to confirm that the efficacy of the operation in terms of weight loss and treatment of comorbid medical problems is very comparable to RYGB.\textsuperscript{81-83}

TREATING COMPLICATIONS

The most concerning immediate complications for SAGB are similar to those of RYGB. Anastomotic leak presents in a similar fashion, and requires operative intervention in most cases. Endoscopic intervention for small controlled leaks may be considered. Adequate drainage, a stable patient, and favorable anatomy for stent placement and security are all needed, as they are with any situation where a gastrointestinal leak is being treated by stenting. Usually operative intervention to drain the leak, re-suture it if the tissue permits, and creation of a reliable enteral feeding access distally (distal jejunostomy feeding tube) are all indicated.

Stenosis of the gastrojejunostomy, which may occur soon after surgery or in a more delayed course, can be initially treated with endoscopic dilation. Reoperation may be needed for persistent stenosis refractory to dilating. The occurrence of a marginal ulcer leading to stenosis decreases the likelihood that dilation alone will correct the stenosis.

Malabsorption of iron, calcium, and $B_{12}$ are all as concerning after SAGB as they are after RYGB, and must be supplemented and monitored long-term postoperatively.

Revisional Procedures

Revision of all of the major procedures listed above is well documented in the literature. Some procedures are more commonly revised than others. The indications for revision are largely grouped into two types: either as a result of a complication of the operation requiring revision, or as a result of poor efficacy of the operation and either poor weight loss or weight regain. The
former group of problems has largely been discussed in the sections regarding treatment of complications of these procedures. This section deals with the revision of procedures for poor efficacy or weight regain.

In general, this author takes a relatively stern approach to revisional surgery. Based on years of experience, my general philosophy of offering revisional surgery is as follows: If the patient has had a bad or ineffective operation, then a revision is indicated. If the patient has had overall poor weight loss or weight regain after a soundly performed operation, and the reason for weight regain is noncompliance with recommended diet and exercise plans, then revisional surgery is not offered. It should be pointed out that many of my colleagues do not ascribe to this philosophy, and feel revisional surgery should be offered to most patients who fail an operation and have indications based on current weight and medical problems for a metabolic and bariatric operation.

Understanding that these conflicting philosophies exist, the following is a summary of techniques and outcomes of revisional surgery as currently documented in the literature.

**REVISION OF LAP AGB**

The most commonly revised operation at this time is the AGB. Many patients have had the operation revised and had the band and port either entirely removed or removed and a second metabolic and bariatric operation performed. One recent report suggested approximately 20% of patients who had a lap band in New York have had the band removed.\(^{84}\) There is some controversy as to whether removal of the band is best done as an initial procedure, with revisional surgery done as a second procedure. Data from France showed a higher leak rate when a single-stage rather than two-stage approach was used.\(^{85}\) However, another large series from Germany showed no increase in leak rate for a two-stage approach of conversion of lap band to gastric bypass.\(^{86}\) The German study emphasized, however, that complications for revision of a lap band to a lap gastric bypass were twice that seen for the initial creation of a gastric bypass.

In general, it has usually been shown that there is a higher complication rate for revisional surgery than is present for an initial index procedure to which the patient is being converted. This is not surprising given the fact that the presence of scar tissue makes reoperation always more challenging and
difficult than surgery on virgin tissue. One recent report from the National Surgical Quality Improvement Program (NSQIP) database showed that the conversion of a lap band to a SG had only more minor complications but no increase in major complications versus the index procedure.\textsuperscript{87} These were one-stage conversion operations. Other series have shown a higher incidence of complications for conversion of a lap band to a SG than the initial performance of a lap band, as has a large series reported from the National Inpatient Sample.\textsuperscript{88}

The Altieri study suggested that more patients had conversion of their lap band to a gastric bypass than to a sleeve gastrectomy. The data have also shown that conversion of a lap band to RYGB is associated with better postoperative weight loss than conversion to a SG.\textsuperscript{89} Twelve- to 24-month follow-up of excess weight loss for SG was 22%, whereas it was 58% for RYGB. Interestingly, conversion to DS after failed lap band was associated with lower EWL at 1 year than RYGB but higher at 2 years (78.4% EWL).

Conversion of SG to RYGB has been generally done mainly for problems of GERD and stenosis. However, some patients who have failed to lose adequate weight after SG have been converted successfully to RYGB. Conversion of SG to DS is also a relatively commonly employed option for those patients who fail SG from a weight loss perspective and who are felt by a surgeon to warrant conversion to an operation that adds malabsorption to the already present restriction of the gastric sleeve.

Revision of RYGB has been a controversial topic for many years. With its long track record, it is well established that approximately 20% to 35% of patients undergoing RYGB will regain a substantial amount of weight. Our 10-year review of patients undergoing RYGB showed the %EWL for the group at 1 year of just over 70% to a 10-year value of 52%.\textsuperscript{48} The weight loss was maldistributed between a smaller fraction of patients regaining a significant amount of weight versus the majority of patients regaining little weight. Given that as many as one-third of patients may regain enough weight to qualify for metabolic and bariatric surgery, the options used by surgeons in the past have included relatively low invasive procedures such as endoscopic suturing of the gastrojejunostomy or adding a band around the gastric pouch, and more extensive revisions including long limb gastric bypass, in which the Roux limb is made significantly longer and the biliopancreatic limb anastomosed to it much more distal and closer to the
ileocecal valve, and conversion to a DS type procedure. The latter two procedures produce significant designed malabsorption. Excess weight loss from a combination of both restriction and malabsorption has been reported in this setting, and is a small but potential danger for any such patient. Careful follow-up is needed after all such operations.

To date, most revisional endoscopic procedures to narrow the gastrojejunostomy after RYGB have been associated with modest amounts of weight loss. Sclerotherapy has been tried using a variety of methods, and has been generally abandoned for poor long-term results. Endoscopic suturing has been performed for over a decade. Initial reports of modest success with a few patients have not been followed up with long-term results showing efficacy. A relatively recent report showed 15% to 20% of EWL in the first 6 months in an 11-center trial using a suction type suturing device (transoral outlet reduction [TRORe] procedure). This actual amount of weight though averaged only 4.5 kg. This device is no longer on the market due to lack of efficacy. An endoscopic device to narrow gastric pouch size, the StomaPhyX device, has been withdrawn from the market after results showing 10 kg weight loss at 1 year. Improved suturing devices are now available for such procedures, and long-term data after their use for anastomotic narrowing is pending.

Adding a band to the pouch of a RYGB has been advocated by some surgeons as part of the primary procedure. Data from one such series showed a 7% improvement in EWL at 1 year; however the actual comparison between banded and non-banded RYGB patients weight loss was not statistically significant. Prevention of weight regain or weight loss after adding a band to a failed RYGB have been reported, but to date this option has not gained much popularity in terms of a revisional operation.

In general, measures that are advocated prior to and after any major revisional metabolic and bariatric surgery include the following:

1. A thorough evaluation of the causes for the patient to regain weight or not lose the expected weight, and therapies to address those causes in addition to surgical reintervention
2. A detailed outline of the current alimentary tract anatomy including upper GI, CT if indicated, and upper endoscopy to evaluate the current anatomy after the patient’s previous surgery
3. A copy of old medical records about the index operation and its details
4. Incorporation of a multidiscipline team approach to the care of the patient, even more so than at the index operation
5. Thorough and complete follow-up, especially if the revisional operation creates an element of malabsorption

**Endoscopic Procedures**

Endoscopic procedures to address weight loss have recently gained considerable popularity relative to their use a decade ago. Most of these procedures are still not considered conventional treatment for morbid obesity. However, some are approved for use in class 1 and class 2 obesity. A brief summary of these procedures and their reported results to date is given here.

**INTRAGASTRIC BALLOONS**

In 1985, the Garren Edwards intragastric balloon was approved for use in the United States and was placed in a large number of patients in its first few years of availability. However, after 3 years the lack of overall efficacy, weight gain after balloon removal, and an increasing incidence of complications from the balloon caused a reassessment of the device, leading soon thereafter to its withdrawal from the market. The FDA would not approve a gastric balloon again until 2015. In the interim, the BioEnterics Intragastric Balloon (BIB) was used in many other countries, with overall results being a 13.2% total body weight loss (TBWL) at 6 months and a 7.5% early removal rate, 18.3% GERD rate, 2% ulcer rate, 1.4% migration rate, 0.3% obstruction rate, 0.1 perforation rate, and a 0.08% death rate.

In 2015, two intragastric balloons were approved for use in the United States. The Orbera single balloon system and the ReShape dual balloon system both had comparable weight loss in their initial FDA trials, with 7.4% and 7.6% of TBWL, respectively. Both had a high incidence of initial nausea, vomiting, and abdominal pain, and an early removal rate of 7.5% to 9%.

A third balloon, the Obalon balloon, was approved for use in 2017. This balloon can be placed by swallowing a capsule that can then be inflated. Multiple balloons, up to three, can be inserted as part of the therapy.
Endoscopic removal is needed, however. Weight loss is comparable to the other balloons by reports to date.\textsuperscript{102}

The major limitation to the intragastric balloon as currently available is the lack of sustained long-term weight loss. One of the few studies that have followed patients for 5 years has shown excess body weight loss of 42\% at 6 months and only 13\% at 5 years.\textsuperscript{103} Other relative limitations to the appeal of the intragastric balloon include the severe initial symptoms of nausea, vomiting, and abdominal pain, the need for endoscopy to remove or introduce and remove the balloons, and the relatively expensive cost of about $8000 to $12,000 at various centers, which is not usually reimbursed by most insurance carriers.

Other space-occupying intragastric devices are being tested for efficacy. None are FDA approved yet. They include devices that partially obstruct the pylorus (transpyloric shuttle),\textsuperscript{104} the esophagogastric junction (full sense),\textsuperscript{105} or release hydrophilic particles within the stomach to absorb water and swell to occupy space (Gelesis 100).\textsuperscript{106} One device, an endoscopically placed long plastic tube secured at the pylorus and designed to prevent contact of food with the duodenum and proximal jejunum, was initially somewhat successful in improving the manifestations of type 2 diabetes.\textsuperscript{107} However, it has been withdrawn from the market due to an increased rate of intrahepatic abscess.

Another FDS-approved device available for patients with class 1 and 2 obesity is a 30 Fr percutaneous endoscopic gastrostomy (PEG) tube that can be hooked to a suction device after meals to empty much of the ingested gastric contents. Initial reports showed a wide variability in weight loss by patients who had the AspireAssist device placed, with an average of 37.2 +/- 27.5\% of excess weight loss at 1 year.\textsuperscript{108}

In this author’s estimation, the most important endoscopic procedure currently being performed is the endoscopic sleeve gastroplasty (ESG). Relying on the improved suturing capacity of the OverStitch device, intragastric sutures are placed to limit the lumen of the distal and mid stomach to create anatomy quite similar to the SG. The fundus is not sutured, however, due to its thin walls and the potential for injury from sutures placed through the gastric wall in this location. The procedure has mainly been performed for patients with class 1 and class 2 obesity. One recent study showed the procedure produced a durable weight loss for 242 patients at three institutions. The 6-month TBWL of 16.8 +/- 6.4\% increased to 19.8 +
11.6% at 18 months follow-up.\textsuperscript{109} This procedure has not yet been approved for reimbursement by most insurance carriers, and as such is still a cash procedure for patients.

**Special Topics Related to Metabolic and Bariatric Surgery**

**CHOLELITHIASIS**

The presence of gallstones at the time of a metabolic and bariatric index operation has usually been addressed by simultaneous cholecystectomy along with the bariatric operation. While some reports have shown an increased length of stay for performance of cholecystectomy with RYGB,\textsuperscript{110} we have shown that adding cholecystectomy to RYGB is safe, confers a less than 1% complication rate, and does not alter length of hospitalization.\textsuperscript{34} We thus advocate a preoperative or intraoperative ultrasound to screen for the presence of gallstones. Difficult biliary anatomy or exposure of the gallbladder can be an indication to abort the additional elective procedure in favor of a time when, with weight loss, such exposure may be improved. However, we have encountered this situation very rarely.

For the patient who has no gallstones, we currently recommend no prophylactic cholecystectomy and instead that the patient take oral ursodiol, 300 mg bid for 6 months, which has been shown to decrease the incidence of gallstone formation after RYGB to 4%.\textsuperscript{35} Surgeons who perform DS are much more likely to include cholecystectomy as part of the index operation, given the high incidence of gallstone formation after this procedure.

**PREOPERATIVE UPPER ENDOSCOPY**

The performance of screening upper endoscopy prior to metabolic surgery is still controversial. Many series have been published in the literature that describe a high incidence of some pathology found when routine upper endoscopy is performed prior to metabolic surgery.\textsuperscript{111,112} A recent meta-analysis found that surgical therapy was altered in a total of 7.6% of cases based on preoperative endoscopic findings.\textsuperscript{113} The conditions most likely to alter the surgical approach include Barrett esophagus, severe esophagitis or
gastritis, adenomatous polyps of the stomach, or a large hiatal hernia. Upper endoscopy is probably more routinely indicated prior to RYGB, where the gastric and duodenal anatomy will no longer be endoscopically accessible postoperatively. Screening prior to any procedure is generally felt indicated for GERD or a history of GERD-related complications. While routine upper endoscopy probably is the optimal choice for determining any pathology preoperatively, current insurance plans often will not reimburse this procedure unless indications such as GERD are present.

**PREGNANCY**

The data over the years continue to support the fact that metabolic and bariatric surgery procedures are generally very safe in terms of imparting little risk to a woman who becomes pregnant after she has acclimated to the procedure. We advocate our patients use birth control for the first year after surgery, since irregularities in menstrual cycles are the norm, and since conception soon after a procedure such as RYGB can be stressful for the mother, who will often have to be carefully monitored for adequate fluid and nutritional intake, especially during the first trimester. However, there are few reports of any significant morbidity to the fetus in a pregnancy after metabolic and bariatric surgery.

**METABOLIC SURGERY: MORE THAN JUST WEIGHT LOSS**

The emphasis of reports on metabolic and bariatric surgical procedures during the 20th century was clearly on the parameter of weight loss. This defined an operation’s efficacy and success. However, the resolution of comorbid medical problems associated with obesity was certainly documented in many reports of bariatric surgery during that period. The mechanism of improvement of comorbid medical problems was felt to lie largely in the fact that the inciting reason for the problem, obesity, had now been corrected. While this is certainly true to a great extent, the actual mechanisms of why obesity accelerated and increased the presence of some of these medical conditions were and to some extent probably remain poorly understood. The observation that weight loss led to resolution of many of the
comorbid medical problems that existed for severely obese patients seemed to place the logical etiology for the medical problem in the obese state itself.

However, certain observations strained the logic that weight loss alone was responsible for the resolution of comorbid medical problems. The strongest example of this was the fact that patients with type 2 diabetes often resolved their disease after only a few weeks of weight loss. Insulin requirements would disappear within weeks, whereas weight loss was at that time still relatively minor compared to the eventual accumulation of lost weight that would follow in subsequent months. The explanation for this remained unclear. However, its observation was quite clearly documented by Pories and Sugerman, among others.

In the past 20 years, there has been a significant acceleration in the amount of research done to explore this observed phenomenon. Below is a summary of the evolution of that process as well as the currently best accepted theories for how RYGB is so effective in the treatment of type 2 diabetes in severely obese patients.

Recent studies have suggested that there is much more involved in the process of weight loss and maintenance of weight loss after metabolic and bariatric surgery than just simple caloric restriction. Weight loss–independent factors that contribute to the success of bariatric operations have now been shown to include changes in the luminal composition of the gut, changes in postprandial gut hormone secretions, and alterations in energy expenditure seen after bariatric surgery.

The argument against simple mechanical limitation of intake as being the cause of success of bariatric surgery lies in several important observations. For gastric bypass, the size of the gastric pouch and the diameter of the anastomotic opening between the stomach pouch and the Roux limb should correlate strongly with successful weight loss after surgery. However, except for the general concept that too large a gastric pouch will lead to less success after surgery, there is no strict correlation between pouch volume and weight loss success. Nor is there one between anastomotic size and weight loss. Finally, sleeve gastrectomy, though having a significantly larger amount of gastric lumen available for food, produces weight loss that is nearly comparable to that of gastric bypass. In addition, the “malabsorptive” component of gastric bypass, diverting food beyond the duodenum and proximal jejunum, appears to account for little additional weight loss when
comparing gastric bypass to sleeve gastrectomy.

Simple caloric restriction, in the absence of any surgical changes to the gastrointestinal tract, will produce increased hunger. Anyone who has gone on a diet can attest to that. However, after both SG and gastric bypass, patients report an absolute lack of appetite. In some patients, there is almost an aversion to food. While the same aversion process will occur in a patient with a proximal obstruction of the gastrointestinal tract, after bariatric surgery, where no true obstruction exists, this lack of appetite is profound and can last many months, sometimes the better part of a year. In most individuals, appetite does eventually return. The process whereby this occurs within the CNS and the gut may hold the secret to satiety, probably the factor that is most aberrant in the disease state of morbid obesity.

Processes that have been implicated as being important in altering the metabolic process in terms of overall caloric intake as well as specific improvement in glucose disposal and insulin sensitivity include an alteration in the secretion of certain gastrointestinal hormones following bariatric surgery. The best studied of these metabolic changes for a specific disease to date involves the alterations in metabolism causing the rapid reversal of diabetes seen after gastric bypass.

It was observed decades ago that type 2 diabetes resolved much more quickly after RYGB than after other operations which eventually produced equal weight loss. Bypassing the duodenum was felt to be the key element in that rapid reversal. This spawned a generation of research about the enteric relationship to glucose metabolism. Rubino showed convincingly in a seminal paper that the creation of a gastric bypass in an obese rat species eliminated the diabetes present. The diabetes returned when the operation was reversed. Further work on the role of the proximal gut in influencing glucose metabolism led to the hypothesis of the pivotal role of glucagon-like peptide 1 (GLP-1) in affecting inulin sensitivity. This was largely accepted for the past decade, but new studies in mice without GLP-1 receptors show gastric bypass remains as effective in altering glucose metabolism. Sleeve gastrectomy has also been shown to be effective, though not as effective as gastric bypass, in reversing type 2 diabetes in morbidly obese patients. Enhanced GLP-1 secretion after SG would not be on the basis of duodenal diversion of food contents. Thus, although much evidence implied an important role for GLP-1 in affecting the rapid reversal of diabetes after
gastric bypass, its incretin effect is probably not the only factor at work in the overall process.

Other gastrointestinal hormones have been implicated in the improvement in carbohydrate metabolism after bariatric surgery. Glucose-dependent insulinotropic peptide (GIP), also found more densely in the proximal gut, has been implicated in improved glucose metabolism, but a clear physiologic role has not been established. Peptide YY, found in the ileum, and known as the “ileal brake” has been hypothesized to produce improved weight loss after gastric bypass and sleeve gastrectomy. PYY release is stimulated by undigested food contents in the mid to distal small bowel. It has a metabolite that has been shown to be a very powerful appetite suppressant through interaction with the hypothalamus in animal models. Its upregulation in mice is associated with improved glucose metabolism. This may best explain its contributory role to the success of RYGB and SG in improving weight loss and glucose metabolism.

Other less well known and less extensively studied hormones may also add some component to the incretin effect seen after oral glucose administration after RYGB. These include oxyntomodulin, which appears to act on the GLP-1 receptor and produces weight loss when injected in obese humans, and gustducin, which acts to stimulate GLP-1 secretion as well.

Insulin sensitivity improves after RYGB due to increased release of insulin in response to the rapid emptying of glucose into the intestine in the absence of any pyloric regulation of gastric emptying. Sleeve gastrectomy has also been shown to have more rapid gastric emptying as well after a period of adaptation, and the same insulin surge has been documented. As animals lose weight, it has also been clearly shown that there is a weight-loss related increase in insulin sensitivity as time passes after surgery. This increased sensitivity likely has two components, one a more rapid one unrelated to weight loss and another related to weight loss. Studies performed using a glucose clamp technique, which allow differentiation of sensitivity to hepatic versus peripheral insulin, have shown that the initial improvement in glucose metabolism after RYGB is that of increased tissue sensitivity to hepatic insulin release. Skeletal muscle increased insulin sensitivity only occurs after some weight loss, thereby being a later component of the overall insulin sensitivity. Another component of the improved glucose
metabolism after RYGB and probably SG also is the increase in pancreatic beta cell mass following these operations.\textsuperscript{129} Current hypotheses suggest that the increased secretion of GLP-1 and GIP are largely responsible for these increases in beta cell mass, which in turn increases the insulin response to a glucose challenge.

The microbiota of an individual is defined as the composition of all the bacteria found within the gut lumen of that individual. The human microbiota and its corresponding genetic component, the microbiome, is only now beginning to be studied and appreciated for its impact on health and disease of the individual. Changes in the microbiota following bariatric surgery have been well documented. These include a decrease in Firmicutes species and an increase in Bacterioides species\textsuperscript{130} as well as an increase in Proteobacteria.\textsuperscript{131} Alterations in the gut flora are felt to be important contributors to metabolism and energy expenditure, as evidenced by the fact that fecal transplants from obese humans or obese mice into germ-free mice showed weight loss compared to germ-free mice receiving fecal transplants from non-obese humans or mice.\textsuperscript{132,133} The mechanisms for such action of the microbiota on the host energy metabolism and weight loss are as yet undefined.

The microbiota do control the composition of circulating bile acids. This may be a mechanisms by which these changes may be affected. It is known that alterations in the microbiota will produce alterations in the type and amount of circulating bile salts in the enterophepatic circulation. Bile salts and their interactions on hepatic lipid absorption and glucose disposal may be important regulators of metabolism and weight after bariatric surgery. It has been shown that bariatric surgery alters bile acid composition, and that diversion of bile surgically into the distal intestine in rats produces weight loss and improved glucose metabolism without any alteration of the stomach or proximal GI tract.\textsuperscript{134} Taurine conjugated bile acids are increased after bariatric surgery, both for sleeve and bypass operations.\textsuperscript{135} In animal models after sleeve gastrectomy, increased amounts of circulating bile acids were found to correlate best with weight loss postoperatively, as well as with improvements in hepatic steatosis. Sleeve gastrectomy improved hepatic steatosis better than simple low calorie restriction weight loss, showing the likely enhanced effects of SG on hepatic fat metabolisms likely affected by alterations in the bile salt pool.\textsuperscript{136} Further studies on the effects of alterations in bile salt pool
composition and action on metabolism are ongoing, with the goal of determining the mechanism of how alterations in bile salts in turn affect glucose and fat metabolism. The alterations in the bile salt pool appear to be related to alterations in the microbiota as a secondary effect of bariatric surgery. This is a rapidly expanding area of current research and likely will yield important further data to help explain the gross changes in body weight seen in animal models when gut flora is altered.

SUMMARY

The disease of morbid obesity is finally recognized as a disease entity in itself. It usually has accompanying diseases that present with increasing frequency as the duration of the obese state continues. For the person with morbid obesity, surgery currently represents the only successful treatment for both the disease of obesity and its related co-morbidities. To date, the field of bariatric surgery is about 65 years old. The frequency of performance of bariatric operations increased dramatically at the turn of the century, corresponding to the availability of laparoscopic approaches to operations. Dramatic improvements in the safety and efficacy of bariatric operations during the past 15 years have resulted in the fact that currently bariatric surgical procedures are among the safest of abdominal operations performed, rivaling appendectomy and elective cholecystectomy for low mortality rates. During that same time frame, there has been increased recognition of the metabolic improvements to patients as a result of bariatric operations, confirming the concept that these operations are not only bariatric but metabolic in effect. Increased study of the mechanisms that promote and preserve the metabolic and bariatric effects of these procedures has also occurred during this time frame, leading to improvements in our understanding of some of these mechanisms and discovery of other as yet barely investigated mechanisms which appear to play important roles as well. It is safe to say that in future years, this research will lead to better optimization of interventional procedures that are metabolically beneficial to patients suffering from the diseases of obesity and its comorbid associated medical diseases. Similarly, based on the increased frequency of newer less invasive procedures and endoscopic approaches to procedures, it is also likely that the procedures of the future will be less invasive and more effective in reversing these disease processes. It is certainly hoped that this occurs, for to
date the acceptance of metabolic and bariatric surgery remains low by the
general population, and its embrace by the medical community is still
incomplete. Obesity continues to increase as a health problem, and a costly
one. Innate biases against obesity remain within the perception of the public
and even within health care providers. We have not yet reached the crucial
tipping point of appeal and efficacy of interventions being popular enough so
that they are used in significantly higher frequency to promote improvements
in the metabolic process of obesity such that this disease and its related
associated diseases become health care issues of decreasing importance. That
remains the goal of metabolic and bariatric surgeons and bariatric medical
physicians and researchers for the immediate future.

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101. ([https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140012b.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140012b.pdf)).


INTESTINE AND COLON
Bowel obstruction vexed medical practitioners as long ago as 350 BC, and it continues to do so today. The management of patients with bowel obstruction is challenging because decision-making is complicated in many patient care scenarios. First, the diagnosis of bowel obstruction may be difficult in a patient who recently underwent surgery. That is, does this lack of gastrointestinal function represent an ileus or a true bowel obstruction? Second, the timing of surgical intervention may not be obvious. When is an operation appropriate in a patient who underwent recent surgery? Finally, what is the appropriate operation in patients who have had multiple, chronic intestinal obstructions? All of these scenarios represent high-risk decisions, and thus management of bowel obstruction requires critical analysis and decision-making. The goal of this review is to provide a contemporary summary of the epidemiology, diagnosis, and management of bowel obstruction in a broad context of impaired gastrointestinal function.

DEFINITION
Bowel obstruction is defined by the lack of aborad transit of intestinal contents, regardless of etiology. Bowel obstruction may involve only the small intestine (small bowel obstruction), the large intestine (large bowel obstruction), or both via systemic alterations in metabolism, electrolyte balance, or neuroregulatory mechanisms (generalized ileus). Traditionally, the surgeon’s perspective of a bowel obstruction represents a mechanical obstruction that is due to physical stenosis or occlusion of the intestinal lumen. In the broader context, however, ineffective motility, without any physical obstruction, causes a functional obstruction or ileus of the intestine. Furthermore, intestinal obstruction can be classified based on duration of presence (acute vs chronic obstruction), extent (partial vs complete), type of obstruction (simple vs closed-loop), and risk of bowel compromise (incarcerated vs strangulated).

Bowel obstruction continues to be one of the most common intra-abdominal problems faced by general surgeons. In a 2010 global burden of disease study, bowel obstruction and ileus were responsible for 2.1 deaths, 54 years of life lost, and 54 disability-adjusted life-years per 100,000 population, respectively, second only to peptic ulcer disease for all abdominal conditions for each of these parameters. Independent of the underlying etiology, bowel obstruction remains a major cause of morbidity and mortality. Early recognition and aggressive treatment are crucial in preventing irreversible ischemia and transmural necrosis, thereby decreasing mortality and long-term morbidity. Despite multiple recent advances in diagnostic imaging and marked advances in our treatment armamentarium, intestinal obstruction will remain a significant surgical problem given the lack of treatment options to manage adhesions, hernias, and malignancies.

**Mechanical Bowel Obstruction**

*Mechanical bowel obstruction* is defined as a physical narrowing or occlusion of the intestinal lumen. This blockage may be intrinsic or extrinsic to the wall of the intestine or secondary to luminal obstruction arising from intraluminal contents (eg, an intraluminal gallstone or other foreign body) *(Table 38-1)*. Partial obstruction implies that the intestinal lumen is narrowed, and some intestinal content can transit distally. In the presence of a complete obstruction, the lumen is obliterated, and no intestinal content can pass beyond the point of obstruction. The risk of strangulation, that is, vascular
compromise of the intestine, increases markedly in the presence of a complete obstruction, especially when caused by an extraluminal etiology such as a hernia defect or an adhesive band compressing the small bowel mesentery. Accordingly, complete obstruction can be categorized further as simple, closed-loop, and strangulated obstruction. A simple obstruction has no associated vascular compromise, and the intestine can be decompressed proximally. Closed-loop obstruction occurs when both ends of the involved intestinal segment are obstructed (eg, volvulus or compressive adhesive bands), and results in increased intraluminal pressure secondary to increased intestinal secretion and accumulation of fluid in the involved intestinal segment. Closed-loop obstruction carries a substantial risk of vascular compromise and irreversible intestinal ischemia of the involved bowel, and thus requires emergent operative attention. Finally, strangulation occurs when the blood supply to the affected intestinal segment is compromised, leading to focal or segmental transmural necrosis. The affected segment may involve only a portion of the bowel wall compressed by a tight adhesive band or an entire intestinal segment as occurs with a strangulated hernia or a closed loop. If viability of the bowel is maintained after relief of the obstruction, strangulation can be reversed (reversible strangulation obstruction). In contrast, irreversible strangulation occurs if the vascular compromise has caused irreversible transmural necrosis whether or not the strangulation is relieved. All irreversible strangulated obstructions start as reversible strangulated obstructions, and thus early diagnosis is paramount to rescuing compromised intestine.

**TABLE 38-1: MECHANICAL BOWEL OBSTRUCTION**
<table>
<thead>
<tr>
<th>Lesions Extrinsic to the Intestinal Wall</th>
<th>Lesions Intrinsic to the Intestinal Wall</th>
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</thead>
<tbody>
<tr>
<td><strong>Adhesions</strong></td>
<td><strong>Congenital</strong></td>
</tr>
<tr>
<td>Postoperative</td>
<td>Intestinal atresia</td>
</tr>
<tr>
<td>Congenital</td>
<td>Meckel’s diverticulum</td>
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<tr>
<td>Postinflammatory</td>
<td>Duplications/cysts</td>
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<td><strong>Hernia</strong></td>
<td><strong>Inflammatory</strong></td>
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<tr>
<td>External abdominal wall</td>
<td>Crohn’s disease</td>
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<tr>
<td>(congenital or acquired)</td>
<td>Eosinophilic granuloma</td>
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<tr>
<td>Internal</td>
<td><strong>Infections</strong></td>
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<tr>
<td>Incisional</td>
<td>Tuberculosis</td>
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<tr>
<td><strong>Congenital</strong></td>
<td><strong>Actinomycosis</strong></td>
</tr>
<tr>
<td>Annular pancreas</td>
<td>Complicated diverticulitis</td>
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<tr>
<td>Malrotation (rotational abnormality)</td>
<td>Appendicitis</td>
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<tr>
<td>Omphalomesenteric duct remnant</td>
<td><strong>Neoplastic</strong></td>
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<tr>
<td><strong>Neoplastic</strong></td>
<td>Primary neoplasms</td>
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<tr>
<td>Carcinomatosis</td>
<td>Metastatic neoplasms</td>
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<td>Extraintestinal neoplasm</td>
<td><strong>Miscellaneous</strong></td>
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<td><strong>Inflammatory</strong></td>
<td>Intussusception</td>
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<tr>
<td>Intra-abdominal abscess</td>
<td>Endometriosis</td>
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<td>“Starch” peritonitis</td>
<td>Radiation enteropathy/stricture</td>
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<td><strong>Miscellaneous</strong></td>
<td>Intramural hematoma</td>
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<td>Volvulus</td>
<td>Ischemic stricture</td>
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<td>Gossypiboma</td>
<td><strong>Intraluminal/obturator obstruction</strong></td>
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<td>Superior mesenteric artery syndrome</td>
<td>Gallstone</td>
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<td>Enterolith</td>
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<td>Phytobezoar</td>
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<td>Parasite infestation</td>
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<tr>
<td></td>
<td>Swallowed foreign body</td>
</tr>
<tr>
<td></td>
<td>(magnets, illicit drug mules,</td>
</tr>
<tr>
<td></td>
<td>sharp objects that perforate the bowel,</td>
</tr>
<tr>
<td></td>
<td>etc)</td>
</tr>
</tbody>
</table>

**Functional Bowel Obstruction or Ileus**

Functional obstruction or ileus occurs when the bowel, small or large, fails to propel content distally in the absence of a mechanical obstruction. The pathophysiology of ileus involves electrolyte disturbances, impaired neuroregulatory innervation, imbalanced hormonal input, and other less common causes (Table 38-2). The most common form of functional bowel obstruction is postoperative ileus, because it is present to some extent after nearly all intra-abdominal operative procedures. Various types of extra-abdominal medical and surgical conditions may also cause a transient functional ileus. Besides these more frequent forms of functional bowel obstruction caused by a response to local or systemic stimuli, there is a group of rare, chronic, progressive, gastrointestinal (GI) “pseudo-obstructions.” These rare forms of functional obstruction are related either to hereditary or acquired visceral myopathies, visceral neuropathies, or a poorly understood disruption of myoneural coordination of organized contractile activity.

**TABLE 38-2: FUNCTIONAL BOWEL OBSTRUCTION, ILEUS, AND PSEUDO-OBSTRUCTION**
<table>
<thead>
<tr>
<th>Intra-Abdominal Causes</th>
<th>Extra-Abdominal Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrapерitoneal problems</strong></td>
<td><strong>Thoracic problems</strong></td>
</tr>
<tr>
<td>Peritonitis (chemical infections)</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>Severe congestive heart failure</td>
</tr>
<tr>
<td>Contained anastomotic leak</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Postoperative (physiologic)</td>
<td>Thoracic trauma</td>
</tr>
<tr>
<td>Chemical:</td>
<td><strong>Metabolic abnormalities</strong></td>
</tr>
<tr>
<td>Gastric juice</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Bile</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Blood</td>
<td>Lead poisoning</td>
</tr>
<tr>
<td><strong>Autoimmune:</strong></td>
<td>Porphyria</td>
</tr>
<tr>
<td>Serositis</td>
<td>Hyperglycemia/ketoacidosis</td>
</tr>
<tr>
<td>Myositis</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Uremia</td>
</tr>
<tr>
<td><strong>Intestinal ischemia:</strong></td>
<td><strong>Medicines</strong></td>
</tr>
<tr>
<td>Arterial or venous</td>
<td>Opiates</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td><strong>Retroperitoneal problems</strong></td>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>Alpha-adrenergic agonists</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Psychotropic drugs</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Catecholamines</td>
</tr>
<tr>
<td>Retroperitoneal trauma/ hematoma</td>
<td><strong>Acute spinal cord injury</strong></td>
</tr>
</tbody>
</table>

Postoperative ileus represents the most common cause of delayed hospital discharge after abdominal operations. The duration of postoperative ileus may correlate with the degree of surgical trauma or the type of operation, and might even be considered a “physiologic” response. A prolonged “pathophysiologic” postoperative ileus may develop in patients operated on for radiation enteropathy, chronic obstruction, or severe peritonitis. Recovery from ileus after manipulation and local trauma differs among anatomic segments of the gastrointestinal tract. Generally, the small bowel recovers effective motor function within hours after an abdominal operation and, in fact, transient focal intestinal peristalsis is often visualized during an abdominal operation. In contrast, the stomach regains motor function 24 to 48 hours after an operation leading to delayed gastric emptying. The colon exhibits the slowest recovery response and may take 3 to 5 days to recover effective propulsive activity postoperatively. Differentiation of postoperative ileus from early postoperative mechanical bowel obstruction is important, because these anomalies are caused by different pathophysiologic mechanisms. In ileus, there is a prolonged inhibition of coordinated bowel activity that can take days or even weeks to resolve, depending on the etiology. The process of impaired postoperative peristaltic activity and coordinated aborad propulsion may be improved by the administration of alvimopan, a peripherally acting μ-opioid receptor antagonist, which has been shown to decrease the incidence of ileus and shorten hospital length of stay.

**Early Postoperative (Mechanical) Bowel Obstruction**

*Early postoperative bowel obstruction* is defined as bowel obstruction occurring within the first 6 weeks postoperatively. This type of intestinal obstruction represents a distinct clinical entity with a unique pathophysiology, and it should be differentiated from both the classic mechanical bowel obstruction as well as from postoperative ileus. The formation of acute adhesions is the responsible cause in over 90% of early postoperative bowel obstructions necessitating surgical management. Other causes include internal herniation, fascial herniation especially after laparoscopic surgery, intra-abdominal abscess, intramural intestinal hematoma, and anastomotic edema or leak. The differential diagnosis is
difficult as it may not be easy or possible to differentiate early postoperative mechanical obstruction from postoperative ileus. Nausea, vomiting, abdominal distention, and obstipation are themselves relatively common findings in the early postoperative period and are alone not distinguishing features of mechanical obstruction. Because the initial symptoms of early postoperative mechanical obstruction tend to be vague, patients are often considered to have ordinary postoperative ileus. Pain secondary to the recent incision, and masked by the use of narcotic analgesics, makes the physical examination often unreliable as well. Interpretation of imaging studies may be difficult, because early postoperative bowel obstruction and ileus can present with similar findings on plain abdominal radiographs. Computed tomography (CT) and contrast studies can help differentiate patients who can be treated conservatively from those who may need operative intervention, especially those with either a focal site of obstruction or the presence of dilated proximal and decompressed distal small bowel; the latter defines a mechanical etiology.

EPIDEMIOLOGY

In recent decades, the overall incidence of small bowel obstruction has been stable over time as noted by a study that examined the incidence from 1988 to 2007 when it ranged from 579 to 654 diagnoses for bowel obstruction per 100,000 population. The etiology of obstruction has not changed during the study period as adhesions remained the most common etiology. The etiology and frequency of obstruction, however, was altered markedly throughout the 20th century when repair of hernias became commonplace, and thus the etiology of bowel obstruction related to incarceration in a hernia defect decreased and was replaced by adhesive obstruction as the most common cause of bowel obstruction. In the underdeveloped world, however, bowel obstruction still manifests with a clinical picture resembling that found in the early 20th century in Western societies, with incarcerated hernias leading the list in frequency. The wider application of minimally invasive surgical procedures with fewer adhesions may decrease the frequency of bowel obstruction secondary to postoperative adhesions, particularly in cholecystectomies and hysterectomies. However, a review by Barmparas and colleagues concluded that while laparoscopic colectomies lowered incidence
of adhesions, this did not correlate to a lower incidence of adhesive small bowel obstruction. Nonetheless, access to improved surgical care in lower middle-income countries will change the etiology of bowel obstruction and improve care.\(^8\)

Obstetric, gynecologic, and other pelvic surgical procedures represent important etiologies for the development of postoperative adhesions.\(^9\) Therefore, it is not surprising that a slightly greater frequency of bowel obstruction is observed in women.

About 80% to 90% of bowel obstructions occur in the small intestine; the other 10% to 20% occur in the colon. Colorectal cancer is responsible for 60% to 70% of all large bowel obstructions, while diverticulitis and volvulus account for the majority of the remaining 30%. In contrast, small bowel obstruction is most commonly attributed to adhesions, abdominal wall hernias, or neoplasms in most advanced Western societies.

Resources expended and costs incurred in the treatment of intestinal obstruction represent a substantive burden on the national health care system of any country. Surprisingly few contemporary data exist regarding the burden of costs for bowel obstruction over a large population regardless of etiology. Most studies are small, with less than 200 patients, and examine only one etiology of obstruction in a defined population. One dated study, however, estimated that adhesive bowel obstruction accounted for over 1 million days of inpatient care and $1.33 billion in health care expenditures in the United States in 1994.\(^9\) Indeed, it has been estimated that 1% of all hospitalizations, 3% of emergency surgical admissions to general hospitals, and 4% of major celiotomies (about 250,000) are undertaken because of bowel obstruction or procedures necessitating adhesiolysis.\(^9\) Another study showed that between 12% and 17% of patients who have undergone a total colectomy are admitted for small bowel obstruction within 2 years of their index operation, while approximately 3% will require an operation to treat an established small bowel obstruction.

Bowel obstruction results in substantial overall mortality and morbidity. Depending on the clinical setting and the presence of related or unrelated comorbidities, mortality rates range from up to 3% for simple obstructions to as great as 30% when there is vascular compromise or perforation of the obstructed bowel. Further, bowel obstruction is frequently a recurrent problem, adding to the overall morbidity of an operation or even repetitive
successful nonoperative management. Recurrence rates vary according to method of management (conservative or operative). Intestinal obstruction recurs in about 12% of patients after a successful primary conservative treatment and in 8% to 32% of patients after operative management for adhesive bowel obstruction. Another study showed that while operatively treated patients had a decreased frequency of recurrence and a greater time interval to recurrence, they also had a greater hospital stay than patients treated conservatively. Also, there was no significant difference in incidence, type of treatment, or type of prior operative procedure among patients presenting with early or late small bowel obstruction. In this study, none of the analyzed variables were predictive of success of a particular treatment.\textsuperscript{10}

\section*{PATHOPHYSIOLOGY}

Mechanical bowel obstruction results in numerous alterations of the normal intestinal physiology, including motility and absorption. The pathophysiology of bowel obstruction remains incompletely understood despite numerous investigations both clinically and experimentally. Bowel distension, decreased absorption, intraluminal hypersecretion, and alterations in motility are found universally, but the mechanisms mediating these relatively dramatic pathophysiologic derangements remain unclear. In addition, bowel obstruction is accompanied by considerable disruption of mechanisms of neural and hormonal control, the type and quantity of endogenous bacterial flora, and the innate immunity of the gut.

The older, classic literature addressing the pathophysiology of bowel obstruction considered a decrease in blood flow as the sentinel event leading to most of the observed pathophysiologic changes. More recent experimental work, however, suggests that an increase in blood flow in association with an intense intramural inflammatory reaction and subsequent mucosal production of reactive oxygen species mediate many of the pathophysiologic changes observed in the early phase of bowel obstruction.\textsuperscript{11}

\section*{Distension, Absorption, and Secretion}

Bowel distension is a characteristic, fundamental, and constant pathophysiologic response to mechanical bowel obstruction. Accumulation of
swallowed air is responsible for much of the small bowel distention in the early phases of obstruction. As would be expected, intraluminal gas consists of approximately 75% nitrogen in the obstructed bowel. Fermentation of sugars, production of carbon dioxide by interaction of gastric acid and bicarbonates from pancreatic and biliary secretions, and diffusion of oxygen and carbon dioxide from the blood are other sources of gas in early obstruction. Dilation and inflammation of the bowel wall cause accumulation of activated neutrophils and stimulation of resident macrophages within the muscular layer of the bowel wall, impairing secretory and motor processes by release of reactive proteolytic enzymes, cytokines, and other locally active substances. Local release of nitric oxide, a potent inhibitor of smooth muscle tone and contractility by the inflammatory response, aggravates intestinal dilation through inhibition of contractile activity. Notably, a correlation between the amount and activity of nitric oxide synthase, the enzyme responsible for nitric oxide synthesis, and the severity of intestinal dilation observed exists. Furthermore, experimental data demonstrate a relationship between distention and the intramural production of reactive oxygen metabolites. In addition to disrupting gut motility, these metabolites also modulate permeability of the vasculature and the gut mucosa.

Along with the intraluminal accumulation of gas, the bowel also has a secondary decrease in net absorption resulting in the addition of water and electrolytes into the lumen during the first 12 hours of small bowel obstruction. By 24 hours, intraluminal water and electrolytes accumulate more rapidly because of a further decrease in absorptive flux; this decrease in net absorptive reflux occurs via stimulation of a concomitant increase in net intestinal secretion (secretory flux). These changes are caused by increased permeability due to secondary mucosal injury resulting in intraluminal leakage of plasma, electrolytes, and extracellular fluid. Whether associated neural or systemic humoral/hormonal mechanisms aggravate this upregulation of unidirectional secretory flux also remains likely but poorly investigated or explained.

This net secretion of fluid into the lumen of the obstructed bowel is exacerbated further by the accumulation of intraluminal bacteria-derived toxins, bile acids, prostaglandins, vasoactive intestinal polypeptide, and mucosa-derived oxygen-free radicals. With a more chronic obstruction, bacterial proliferation occurs in the lumen, further disrupting absorption, secretion, and mucosal integrity. The decrease in the absorptive capacity and
increase in secretion lead to important fluid losses (enterosecretion) that may result in profound dehydration. Although the intestinal wall distal to the obstruction maintains relatively normal function, the inability of luminal content to reach the unobstructed small bowel and colonic absorptive surface is an important component of overall dehydration.

### Intestinal Motility

In an attempt to propel intraluminal contents past the obstruction, intestinal contractile activity increases in the early phase of bowel obstruction, probably in large part related to the intestinal distention. Later in the course of the bowel obstruction, however, contractile activity decreases likely secondary to a relative hypoxia of the intestinal wall and enhanced intramural inflammation. Although the exact mechanisms have not been described adequately, these responses may be similar to the changes found early after an abdominal operation, again related to inflammation of the intestinal wall.\(^{12,13}\) Some investigators\(^{14}\) have suggested that the alterations in intestinal motility are secondary to a disruption of the normal autonomic parasympathetic (vagal) and sympathetic splanchnic innervation, while others relate these changes more to a local effect of inflammation of the intestinal wall.

Splanchnic innervation has been the focus of extensive research, and especially so in the pathogenesis of paralytic ileus. Chemical sympathectomy has been successful in ameliorating ileus in several experimental models. Other pharmacologic approaches have focused on blocking the neural inhibitory mechanisms affecting enteric neuromuscular coordination via sympatholytics and cholinergic agonists.\(^{15,16}\) Still other experimental approaches have been designed to prevent or inhibit the inflammatory response that accompanies the “physiologic” response to celiotomy or the abnormal inflammatory response accompanying generalized ileus. More recent investigative attention has been directed to impaired intestinal motility in the face of opioid administration postoperatively.\(^{17}\) The \(\mu\)-receptor antagonist alvimopan appears to inhibit opioid-induced intestinal impairment and enhance motility.

### Circulatory Changes
Bowel wall ischemia may occur through several mechanisms such as extrinsic compression of the mesenteric arcades by adhesions or an axial twist of the mesentery in a hernia defect. Alternatively, progressive distention in the presence of a closed-loop bowel obstruction without mesenteric axial torsion can cause vascular compromise or strangulation. Rarely, extensive mesenteric venous thrombosis leads to compromised arterial inflow and ischemia. During an obstruction, the large bowel obstruction is especially susceptible to vascular compromise and subsequent colonic distention because watershed areas of colonic perfusion represent end organ blood supply. Colonic ischemia is further exacerbated by bacterial proliferation and generation of luminal gas.

Progressive distention of the bowel lumen with a concomitant increase in intraluminal pressure results in increased transmural pressure on capillary blood flow within the bowel wall. The possibility of intestinal wall ischemia presents a real concern in a closed-loop small bowel obstruction, especially in large bowel obstruction when the ileocecal valve is competent and the distended colon cannot decompress retrograde into the small bowel. The resultant increase in intraluminal pressure may compromise blood flow by exceeding venous pressure. This scenario occurs most commonly in the ascending colon where the luminal diameter and resulting wall tension are the greatest. This pathophysiology increases the urgency of treatment response for large bowel obstruction since vascular compromise may occur quickly. This type of bowel wall ischemia may lead to further disruption of intestinal absorption, a relative increase in net secretion, an unregulated increase in mucosal permeability, and intramural production of reactive oxygen species by activated resident and recruited leukocytes. These reactive oxygen species cause peroxidation of the lipid components of the cellular membrane, release of cytokines and other inflammatory mediators, and permit systemic toxicity. With strangulation of the blood supply, blood loss is exacerbated by infarcted bowel, which, together with the preexistent fluid loss, leads to more hemodynamic instability.

**Microbiology and Bacterial Translocation**

The resident and transient flora of the upper small intestine consists mainly of gram-positive, facultative, anaerobic organisms in small concentrations, usually less than $10^6$ colonies/mL. The bacterial count increases distally to
about $10^8$ colonies/mL in the distal ileum. In addition to this increase in number of bacteria, a change of flora to primarily coliform and anaerobic organisms is apparent. In the presence of obstruction, however, a rapid proliferation of bacteria occurs proximal to the point of obstruction, consisting predominantly of fecal-type organisms. The proliferation of this fecal flora, proportional to the duration of obstruction, reaches a plateau of $10^9$ to $10^{10}$ colonies/mL after 12 to 48 hours of an established obstruction. The bowel distal to the obstruction tends to maintain its usual bacterial flora until the onset of a generalized inflammatory-provoked ileus, resulting only then in bacterial proliferation distal to the point of obstruction. Bacterial toxins play an important role in the mucosal response to bowel obstruction. Experiments in germ-free dogs with mechanical bowel obstruction have shown that net intraluminal accumulation of fluid and electrolytes does not occur, and net absorption continues.

Experiments, primarily in rodents, have shown that bacterial translocation occurs secondary to impairment of the barrier function of the intestinal mucosa if bowel obstruction persists. The disruption of the mucosal barrier begins early after the onset of bowel obstruction. The cellular response to obstruction is multifactorial. In the enterocyte, the endoplasmic reticulum dilates as early as 4 hours after onset of bowel obstruction. Mitochondrial swelling, focal epithelial necrosis, intracellular ballooning, and degenerative changes in the nucleus of epithelial cells (apoptosis) have been demonstrated as early as 6 to 12 hours after the onset of obstruction in this experimental model.\textsuperscript{18} The mucosal defense is compromised further by a decrease in perfusion of the intestinal wall. The loss of mucosal integrity allows luminal bacteria to both translocate as well as to invade the submucosa and enter the systemic circulation via the portal venous and lymphatic systems. Several bacterial substances can be retrieved from peritoneal fluid and lymphatic channels even in the absence of perforation. In the rodent model, bacteria can be cultured from the spleen, liver, and mesenteric lymph nodes, indicating a marked increase in bacterial translocation. Concomitant with bacterial translocation, lymph fluid contains numerous bacterial proteins and lipoproteins that further disrupt normal gut function.

The demonstration of bacterial translocation in these elegant studies with rodent models led to the erroneous assumption of the existence of a similar bacterial translocation in humans. Reproducible documentation of true bacterial translocation in man is notably lacking, and existence of a true
bacterial translocation seems unlikely. Several studies have unsuccessfully tried to document the presence of bacteria in intra-abdominal lymph nodes, spleen, liver, and even lymphatics. In contrast, more recent work has shown that lipopolysaccharide and other inflammatory vasoregulatory mediators, but not bacteria, can be recovered from the mesenteric lymphatics. The eventual drainage of these inflammatory substances into the systemic circulation may lead both to the systemic manifestations of sepsis and further disruption of the mucosal barrier function.

The change in the intraluminal bacteriology in simple intestinal obstruction is important clinically, because it markedly increases the risk of infectious complications, especially if an intestinal resection is required or if an inadvertent enterotomy occurs with intraperitoneal contaminated of highly inoculated, bacterial-laden enteric contents. In contrast, with irreversible strangulation obstruction, a myriad of local and systemic alterations, such as systemic entry of bacterial products, activation of immunocompetent cells, release of cytokines, and increased formation of reactive oxygen intermediate, can promote the systemic inflammatory response syndrome and progress to multiple organ dysfunction with all its consequences.

**ETIOLOGY**

**Adhesions**

*Adhesions* are inflammatory-derived, fibrous attachments of connective tissue that adhere to organ surfaces. Adhesions may be congenital or acquired through postinflammatory and/or postoperative processes. Congenital or inflammatory adhesions are less frequent causes of bowel obstruction than postoperative adhesions, except in certain circumstances such as rotational disorders (malrotation) or a persistent urachus. The leading cause of small bowel obstruction in Western societies is postoperative adhesions, which are responsible for 40% to 80% of bowel obstructions in hospitalized patients. This wide variation in incidence of adhesive obstruction varies with referral patterns, community practice settings, racial cultures, and regional preferences.

Adhesion formation is nearly universal after celiotomy and starts within hours of an intra-abdominal operation, since the inflammatory phase is the
first requirement for adhesion development. While the exact pathogenesis of adhesion formation remains incompletely understood, experts agree that adhesion formation is a surface event associated with peritoneal injury. This inciting trauma triggers a local inflammatory response leading to activation of the complement and coagulation cascades along with exudation of fibrinogen-rich fluid; the full establishment of this fibrinous inflammatory response is present 5 to 7 days after the trauma of a celiotomy. Recent findings have identified the presence of sensory nerve fibers in human peritoneal adhesions, suggesting that these structures may be capable of conducting pain or other neural responses.

Peritoneal healing (mesothelialization) appears to differ from the response in skin, where re-epithelialization occurs from the periphery inward. In the peritoneum, operative or traumatic defects are reperitonealized by implantation of mesothelial cells in multiple areas of the defect. This mesothelialization takes place quite rapidly, and resurfacing is often complete by 2 to 5 days after the injury, depending on local conditions.

Normal peritoneal healing, however, is a complex, interrelated, programmed inflammatory process. The initial response involves infiltration of the wound area with polymorphonuclear leukocytes and lymphocytes. During the ensuing 24 to 36 hours, circulating and local macrophages are recruited by various chemokines. By 48 hours, a fibrin scaffold overlying the defect has been established, covered by macrophages and a few mesothelial cells. These mesothelial cells then coalesce to fully cover the defect over the next 2 to 5 days. Fibroblasts and other mesenchymal cells populate the underlying fibrin scaffold and begin to lay down a basement membrane. By 8 to 10 days, a single layer of mesothelial cells resting on a continuous basement membrane has been established, and the underlying reactive matrix and inflammatory cells regress. This process describes the simple resurfacing of an uncomplicated peritoneal defect.

In comparison to the previously described physiologic process of normal peritoneal healing, adhesion formation is a pathologic process. Studies suggest that adhesions form in response to the initial fibrin gel matrix in response to the local, inflammatory microenvironment. This fibrin gel matrix consists of numerous types of cells, including the initial leukocytes, but also other humorally active cells such as platelets, mast cells, and erythrocytes, in conjunction with surgical debris, nonviable tissue, foreign bodies, and
possibly bacteria. The resultant spectrum of fibro-inflammatory changes between physiologic mesothelial healing versus pathologic adhesion formation varies not only among individuals but is dependent also on many other conditions, such as inflammation, infection, devitalized tissue, and foreign bodies.

If the fibrin gel allows apposition of adjacent surfaces, a band or bridge may form (ie, an adhesion). This process of adhesion formation is dynamic, consisting predominantly of macrophages early, but by 2 to 4 days, larger strands of fibrin begin to appear along with fibroblasts. By 5 days, distinct bundles of collagen are apparent, and the fibroblasts begin to form a syncytium within the matrix. These cells predominate thereafter, and eventually the fibrin matrix and cellular elements are replaced by a vascularized, granulation-type tissue containing macrophages, fibroblasts, giant cells, and a rich vascular supply. Eventually, the surface of the adhesions are covered by a mesothelial layer, but only after formation of the underlying fibrous scar leading to surface opposition and transperitoneal fibroinflammatory bands of varying severity and extent.

An important factor in the spectrum of adhesion formation that contributes to the risk of future adhesive bowel obstruction is the type of surgical procedure performed. Operations involving structures in the inframesocolic compartment and those in the pelvic region such as colonic, rectal, and gynecologic procedures impart the highest risk. Open procedures, use of gloves containing starch granules, gallstone spillage during cholecystectomy, and separate peritoneal closure were also correlated with adhesive SBO in a review article. Adhesive bowel obstruction may occur at any time postoperatively after a celiotomy, with reports ranging as early as within the first postoperative month to more than eight decades after the index operation. A study by Menzies and Ellis found that about 20% of adhesive bowel obstructions occur within 30 days after the initial celiotomy, about 20% occur between 1 and 12 months postoperatively, another 20% tend to occur between 1 and 5 years postoperatively, with the remainder (~40%) occurring after 5 years. A Norwegian study of patients requiring an operation for adhesive bowel obstruction found that most episodes of recurrent bowel obstruction occurred within 5 years after the previous episode, but the risk of bowel obstruction persisted for more than 20 years after a prior episode, reaching an incidence as great as 29% at 25 years. Therefore, a common predisposition to adhesive obstruction is the presence of a prior episode of
adhesive obstruction. Numerous surgical attempts to decrease or prevent the
development of postoperative adhesions have been reported and are discussed
subsequently. The literature on pharmacologic prophylaxis against
postoperative adhesion formation is extensive and riddled with numerous
false claims of benefit. Suffice it to say that no reliable or truly effective
pharmacologic agent has been developed to augment mesothelialization and
prevent adhesion formation. Several proprietary barrier products of variable
efficacy have been developed and will be discussed.

**Hernia**

Hernias are the second most common cause of bowel obstruction in most
reported series. Inguinal hernias and hernias acquired postoperatively most
frequently lead to intestinal obstruction, but congenital abdominal wall or
internal hernias may on occasion cause a bowel obstruction by incarcerating
intestinal contents. Hernias as an etiology are more common in males than in
females, primarily because of the predominance of inguinal hernias in men.
In contrast, incarcerated femoral or obturator hernias are more common in
women.

Approximately 5% of external hernias will require emergency operation if
they are not repaired electively. These hernias are usually incisional hernias,
umbilical hernias, and indirect inguinal or femoral hernias. Inguinal hernias
rarely incarcerate, which has changed their management from repair of all
inguinal hernias to a watchful waiting approach in the asymptomatic or
minimally symptomatic patient. The presence of acute incarceration should
prompt emergent operative management, because 10% to 15% of
incarcerated hernias contain necrotic bowel at exploration (Figs 38-1 and 38-2). Chronically incarcerated hernias can develop strangulation, but most
chronically incarcerated hernias can be managed electively.
FIGURE 38-1  Gangrenous bowel from an irreversible, strangulated, incarcerated inguinal hernia.
Internal Hernia after Laparoscopic Gastric Bypass

Minimally invasive surgery has brought new etiologies of intestinal obstruction. The reported incidence of internal hernia after laparoscopic
intestinal surgery, and especially after Roux-en-Y gastric bypass (RYGB), is 0.2% to 3%, a significantly increased incidence compared with the open approach.\textsuperscript{26,27} Factors contributing to the increased risk of internal hernia after a laparoscopic approach include lack of adhesion formation, increased small bowel mobility, marked weight loss–induced increased mesenteric openings, and failure to close all mesenteric defects appropriately. There are two or three mesenteric defects created during laparoscopic RYGB, depending on whether the retrocolic or antecolic technique is used\textsuperscript{28} (Fig. 38-3). Petersen’s defect or space is the best-known site of herniation and can arise with either an antecolic or retrocolic position of the alimentary limb.\textsuperscript{29} It is named after Petersen, who in 1900 described two cases of internal herniation posterior to a loop gastrojejunostomy.\textsuperscript{30} Internal hernias are often difficult to diagnose; indeed, patients with internal hernias present often with nonspecific or intermittent symptoms (periumbilical pain, nausea, vomiting, anorexia, abdominal distention). Spontaneous reduction in the hernia can occur, and CT, upper GI contrast series, and plain abdominal films may be nondiagnostic.\textsuperscript{28} Symptoms of intermittent bowel obstruction after laparoscopic gastric bypass should raise suspicion for the presence of an internal hernia, especially after weight loss. The best measure to prevent these hernias is the meticulous closure of the created mesenteric defects, and suspicion of an internal hernia may itself be appropriate justification for operative exploration, especially via a diagnostic laparoscopy.
FIGURE 38-3 Internal hernia defects after Roux-en-Y gastric bypass (RYGB). A. Retrocolic RYGB; B. Antecolic RYGB. R, Roux limb; ST, stomach. Mesenteric defect at enteroenterostomy (solid arrows), transverse mesocolic defect (open arrow), and Peterson’s hernia posterior to Roux limb mesentery (dashed arrows).

Trocar Site Hernia

The reported incidence of trocar site herniation is 0.2% to 3%; the true long-term incidence, however, might even be greater. Trocar site hernias are observed rarely with 5-mm trocars but more frequently with the use of 10-mm, 12-mm, or bigger trocars and especially with the “cutting” or bladed trocars. Closure of the fascial defect and the use of noncutting, radial expanding trocars are recommended to decrease the risk for formation of trocar site hernias. Trocar site hernias can lead to small bowel obstruction early or late after a minimal access, intra-abdominal procedure.
Following a laparoscopic procedure, patient complaints of pain in the region of a trocar site, nausea, or vomiting should lead to investigation for a bowel obstruction. In these cases, the bowel obstruction may be partial or complete. Commonly, the antimesenteric portion of the bowel wall will be incarcerated in the small fascial defect, resulting in a partial obstruction. These hernias are dangerous, because they may result in strangulation and necrosis in the absence of intestinal obstruction. Reduction of necrotic bowel during hernia repair can result in missed perforation and peritonitis. Although trocar-associated hernias are rare, with the widespread use of laparoscopy, they have become a well-known complication.

**Malignant Bowel Obstruction**

Primary intra-abdominal neoplasms are a common cause of both large and small bowel obstruction. Colorectal, gastric, small bowel, and ovarian neoplasms are the most frequent causes of malignant bowel obstruction, either from the primary lesion (colon and small bowel neoplasms) or from peritoneal metastases (ovarian, colonic, and gastric neoplasms). In many of these patients, bowel obstruction is associated with a high rate of recurrence and morbidity, and may often be a terminal event.

Metastatic cancer can also cause bowel obstruction, usually small bowel obstruction. The most common form of obstructing metastatic lesion is peritoneal carcinomatosis related to one of the aforementioned primary, intra-abdominal malignancies, but localized hematogenous metastases to the wall of the small intestine from melanoma and carcinoma of the breast, kidney, or lung can also cause intraperitoneal metastases that can obstruct the bowel (Fig. 38-4).
Crohn’s Disease

Crohn’s disease is a chronic, transmural, inflammatory ailment of the gastrointestinal tract that may affect any part of the alimentary tract from the mouth to the anus. Despite often intense involvement of the bowel wall, Crohn’s disease is responsible for fewer than 5% of cases of small bowel obstruction. When true mechanical obstruction is present, the cause is usually secondary to the inflammatory process or to chronic stricture formation.

Other granulomatous diseases causing obstruction, such as tuberculosis and actinomycosis, are much less common in Western countries, but in the developing world where acquired immune deficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection are endemic, intra-abdominal tuberculosis must be entertained in the diagnosis of intestinal obstruction.

Intussusception

Intussusception is a relatively frequent cause of bowel obstruction in infancy, but it accounts for only 2% of bowel obstruction in the adult population. The median age of presentation in adults with intussusception is the sixth to seventh decade. The etiology of intussusception differs greatly between adult
and pediatric patients. In the vast majority of adult intussusceptions, there is a
demonstrable inflammatory lesion or a neoplasm that serves as the lead point
of the intussusception; however, up to 20% of adult cases are idiopathic.
Neoplasms causing intussusception in adults are malignant in almost 50% of
patients. Although rare in the Western Hemisphere, intussusception is one of
the most common causes of bowel obstruction in central Africa, for reasons
not yet fully explained.

**Volvulus**

Volvulus represents an axial twist of the bowel and its mesentery. This entity
is an infrequent cause of small or large bowel obstruction in the Western
Hemisphere (Figs 38-5 and 38-6). Volvulus is encountered more frequently
in the geriatric population, in individuals with a long history of constipation,
or in institutionalized, neurologically impaired, or psychiatric patients.
Colonic volvulus comprises about 1% to 4% of all bowel obstructions and
about 10% to 15% of all large bowel obstructions. The volvulated segment
must be mobile to allow the degree of freedom necessary to permit an axial
twist of the mesentery. The affected segment has either an especially long,
narrow mesentery (eg, malrotation or cecal volvulus) and/or a lack of bowel
wall fixation (floppy cecum syndrome).

**FIGURE 38-5** Sigmoid volvulus. A. Supine abdominal radiograph showing
the dilated, volvulated segment of redundant sigmoid colon pointing toward the right upper quadrant; arrows show the space between the sigmoid and hepatic and splenic flexures. B. Contrast enema in sigmoid volvulus showing cutoff at distal site of volvulated sigmoid having a “bird-beak” appearance.

Overall, sigmoid volvulus accounts for 75% of all patients with volvulus. In contrast, cecal volvulus is responsible for the majority of the remaining 25% of bowel volvulus incidences in the United States and is the most common cause of large bowel obstruction in pregnancy. The “cecal bascule” is a unique, though less common, form of cecal volvulus that occurs when the true anatomic cecum (ie, the part of the ascending colon that lies caudal to the
entrance of the ileocecal valve) folds anteriorly over onto the ascending colon, obstructing the lumen. This form of cecal volvulus may be intermittent and recurrent, and is especially difficult to diagnose.

Primary volvulus of the small intestine is extremely rare in the United States but is quite prevalent in central Africa, India, and the Middle East. Speculation about etiology has been related to abrupt dietary changes that occur during the religious holiday when the people celebrating Ramadan fast during the day and then consume a large meal after dark. Some investigators, however, maintain that this racial group has an exceedingly long, floppy small bowel mesentery that permits generous mobility of the small bowel.

**Other Causes**

Numerous other causes of bowel obstruction exist, but these are so uncommon that we list them in *Table 38-1* for completeness but will not discuss them further other than to highlight two unique causes—radiation changes and radiation enteropathy—with images (*Figs 38-7* and *38-8*).
FIGURE 38-7 Radiation changes in distal colon/rectum (arrows).
FIGURE 38-8 Radiation enteropathy. Note the narrowed segments of ileum with much thickened bowel walls (separation between adjacent loops).

**DIAGNOSIS**

The diagnosis of bowel obstruction is highly suspected clinically based on careful history-taking and physical examination, and it may be confirmed by imaging, such as abdominal radiography or CT. The etiology of the obstruction can often be determined by astute history-taking complemented with physical examination and imaging studies.

**History and Physical Examination**
The classic clinical picture of a patient suffering from bowel obstruction includes intermittent crampy abdominal pain, distention, acute obstipation, nausea, and vomiting. Abdominal pain and then distention usually precede the appearance of nausea and vomiting by several hours. The more proximal the obstruction, the earlier and more prominent are the symptoms of nausea and vomiting, while distension is usually less prominent. Conversely, the more distal the obstruction, the more prominent the abdominal distention. Vomiting is relatively uncommon in colonic obstruction until its later stages. The abrupt onset of symptoms makes an acute obstructive cause more likely and may herald the presence of a closed-loop obstruction.

The location and character of pain may be helpful in differentiating mechanical bowel obstruction from ileus. Ileus tends to have a more diffuse and mild pain, often without waves of colic, while mechanical bowel obstruction usually presents as severe, truly colicky pain. Recurrent paroxysms occurring in short (10-30 seconds) crescendo-decrescendo episodes is often associated with mechanical small bowel obstruction, while in mechanical large bowel obstruction episodes are usually spaced farther apart and tend to last longer (1-2 minutes). Pain is usually described as visceral and poorly localized. Classically, the presence of constant or localized pain has been regarded as a sign of strangulation. Several studies, however, have shown that these findings are neither sensitive nor specific for the detection of strangulation.

Obtaining a complete medical history is of paramount importance to make the diagnosis and determine the etiology. The fundamentals of history-taking, including the type and location of pain, the temporal association of symptoms, associated symptoms, and aggravating and alleviating factors, are all important components in obtaining a thorough history. The past medical history may also be critical in both making the diagnosis and establishing the cause of bowel obstruction. It is especially important to inquire about previous episodes of bowel obstruction, recent and distant abdominal operations, current medications, a history of chronic constipation, recent changes in the caliber of stools, and a history of cancer including its stage at presentation and related treatments (operative therapy, chemotherapy, or radiation therapy). Other causes of chronic intestinal obstruction such as Crohn’s disease or other intra-abdominal inflammatory processes should be discussed.

A thorough physical examination is mandatory and should include
assessment of vital signs and hydration status as part of the initial resuscitation. Tachycardia, hypotension, and oliguria are signs of advanced dehydration that mandate aggressive resuscitation. Fever may be associated with an infectious cause or with strangulation. Thereafter, the exam should proceed with abdominal inspection, auscultation, percussion, and palpation. It is important to look closely for potential hernia defects and previous surgical incisions, including inguinal incisions for previous herniorrhaphies. Differential diagnosis should also include the possibility of internal hernias or those “external” hernias not necessarily associated with an obvious bulge, such as obturator, femoral, or intramural Spigelian hernias.

Auscultation can determine the presence, frequency, and quality of the “obstructed” bowel sounds. Bowel obstruction may have the metallic tinkling sounds of “water dripping into a large hollow container,” indicative of dilated bowel with an air–fluid interface. Functional obstruction (ileus) may present with an absence of bowel sounds. Mechanical bowel obstruction presents with an increase in the frequency of bowel sounds, but more specifically the high-pitched “rushes” and “groans” followed by the metallic tinkling sounds. In both mechanical and functional bowel obstruction, a succussion splash may be heard in the presence of a dilated stomach or markedly dilated small bowel filled with an air–fluid interface. The presence of a succussion splash is not normal in a patient who has not eaten or ingested liquids in the previous 1 to 2 hours and should be regarded as an important, abnormal, and often underappreciated sign of bowel obstruction.

Abdominal palpation should reveal the presence of peritoneal signs, such as rebound, localized tenderness, and involuntary guarding that herald vascular compromise or perforation. The presence of these findings is suggestive of the need for an emergent operation. Abdominal masses should be sought and noted. A meticulous search for hernia defects, especially inguinal and femoral hernias, is essential, because they can easily be overlooked. Rectal examination is required to rule out fecal impaction or locate a low-lying rectal cancer as a cause of obstruction.

**Laboratory**

Laboratory tests are essential in patients with bowel obstruction because they may aid in the diagnosis, and more importantly, any underlying metabolic defects should be corrected prior to operative therapy. While no laboratory
test is sensitive and specific enough to diagnose mesenteric ischemia reliably, a spectrum of laboratory tests may be helpful in determining the condition of the patient and should guide resuscitation. A complete blood cell count and differential, electrolyte panel, blood urea nitrogen, creatinine, and urinalysis should be obtained to evaluate fluid and electrolyte imbalance and to assess the possibility of sepsis. Arterial blood pH, serum lactate concentrations, and amylase and lactic dehydrogenase activity may be useful tests in the evaluation of bowel obstruction, especially when trying to exclude the presence of strangulation or underlying bowel necrosis. An increase in serum lactate concentrations should raise the suspicion of intestinal ischemia; however, it is often a late finding. D-dimer was proposed as an early marker of acute mesenteric ischemia, but it appears to be insensitive. Intestinal fatty acid–binding protein (I-FABP) is a highly sensitive marker for extensive mesenteric infarction; however, it does not appear to be sensitive enough to detect more limited intestinal ischemia in strangulated bowel. Some authors have suggested that serum concentrations of phosphate and isoforms of creatine phosphokinase (isoform B), plasma level of ischemia-modified albumin, gut luminal tyrosine concentrations, and α-glutathione S transferase (α-GST) may identify the presence of intestinal cell necrosis. However, the specificity and especially the sensitivity are not accurate enough to base a management decision solely on these parameters.

**Radiologic Findings**

The management of small bowel obstruction remains heavily reliant on excellent clinical acumen and appropriate imaging. The clinician is faced with answering the critical questions, “is this complete obstruction,” and “is the intestine ischemic?” The literature is replete with clinical studies examining the prognostic value of various forms of imaging in terms of predicting the need for operative management or the presence of intestinal ischemia. Most of these series have investigated the role of CT, and we will highlight these findings.

**FLAT AND UPRIGHT ABDOMINAL RADIOGRAPHS**

Plain radiographs, including a chest x-ray and flat and upright films of the
abdomen, remain a valuable initial imaging modality in patients with clinical small bowel obstruction. An initial chest x-ray may reveal extra-abdominal processes such as pneumonia that could be associated with an ileus rather than bowel obstruction. In addition, the presence of free air from a perforated viscus may indicate a diagnosis other than small bowel obstruction or a serious complication of small bowel obstruction requiring emergent treatment.

Flat and upright films of the abdomen in patients with a small bowel obstruction characteristically have multiple air–fluid levels in dilated loops of bowel and a paucity of gas in the distal (decompressed) small bowel and colon (Fig. 38-9). The location of the obstruction in the proximal or distal small intestine, however, greatly influences the findings on the plain abdominal films. A very proximal small bowel obstruction may be associated with films that demonstrate few, if any, air–fluid levels, with a relatively small gastric air–fluid level resulting from a fluid-filled stomach. Conversely, a distal small bowel obstruction will likely have multiple air–fluid levels with dilated loops of small bowel stacked on one another (Figs 38-10 and 38-11). Similarly, the pattern of bowel gas may assist in determining whether the obstruction represents a small or large bowel process. On a plain abdominal film, the small bowel lies centrally, and intestinal markings from the valvulae conniventes or plicae circulars encompass the entire diameter of the bowel, whereas the large bowel lies at the periphery of the abdomen, and haustral markings only partially cross the bowel. Furthermore, the appearance of the bowel gas may also give a clue as to the duration of the obstruction. So-called “fecalization” of the small bowel content, whereby the luminal content shows less of an air–fluid level and more of an appearance of semisolid content with pockets of gas, suggests a more chronic obstruction and may be helpful in supporting the need for operative intervention, not because of worry of strangulation but rather a chronic, established, non-resolving process.
FIGURE 38-9  Supine abdominal radiograph showing an incomplete small intestinal obstruction. Note the dilated loops of small bowel.
FIGURE 38-10 Complete small bowel obstruction. A. Supine abdominal radiograph shows multiple loops of dilated small bowel with colonic gas. B. Upright radiograph shows multiple air–fluid levels in the small intestine (arrows).

FIGURE 38-11 Small bowel obstruction with fluid-filled loops of small bowel in left lower quadrant (arrows).

Rarely, a plain film of the abdomen will contain a pathognomonic sign of intestinal obstruction from gallstone ileus (a misnomer because it is a true mechanical obstruction), as is the case with pneumobilia in a patient with gallstones and no history of biliary instrumentation. Importantly, plain films of the abdomen are notoriously poor indicators of bowel involved with vascular compromise unless the devastating signs of portal venous gas and intestinal pneumatosis are evident. Closed-loop bowel obstructions are also difficult to diagnose on plain x-rays, because the involved bowel with a
proximal and distal occlusion may be fluid-filled and lack any gas. Thus, additional imaging procedures should be obtained in patients with any suspicion of compromised bowel.

CONTRAST STUDIES

Though contrast studies using either dilute barium or hyperosmotic, water-soluble contrast of the small and large bowel have been an integral component of the diagnostic evaluation, enthusiasm for these studies has waned substantially. The radiologic literature and various guidelines developed by the radiologic community support strongly the use of contrast-enhanced CT as the diagnostic imaging modality of choice. Nonetheless, in specific clinical situations, such as in a patient with an obstructing sigmoid or rectal tumor, a radiograph with rectally administered contrast may provide diagnostic information that is timely, economical, and clinically important (Fig. 38-12). On occasion, a small bowel follow-through series may be helpful in distinguishing between mucosal inflammation and extraluminal compromise from adhesions as the etiology of bowel obstruction in a patient with Crohn’s disease. This diagnostic information may alter the therapeutic approach, but generally small bowel followthrough studies have little if any advantage over CT.
FIGURE 38-12  Barium enema showing complete large bowel obstruction in the ascending colon.

When contrast agents are utilized, the risks of each agent must be considered carefully. The primary side effects of barium include inspissation in the obstructed large bowel. Also, barium results in severe intraperitoneal infection/barium peritonitis when extravasated in the face of small intestinal perforation. Gastrografin, if aspirated, can cause a severe pneumonitis; moreover, this contrast agent becomes diluted rapidly with an established
small bowel obstruction, and thereby yields little information in a distal small bowel obstruction. Finally, most surgeons agree that contrast studies are contraindicated in patients with a clear diagnosis of complete bowel obstruction and when strangulation or perforation is suspected.

**COMPUTED TOMOGRAPHY**

In many centers, computed tomography (CT) has become the primary diagnostic imaging modality for the diagnosis of suspected intestinal obstruction, and in fact in some institutions it has replaced plain radiographs as the initial imaging test. The increased use of CT reflects the preference of clinicians for the additional diagnostic information garnered from this examination. CT not only provides information about the presence or absence of a luminal obstruction, but it can also define both the site of obstruction and the existence of extraluminal processes, a small bowel transition point, associated inflammation, fluid collections, masses, abdominal wall or internal hernias, and free intraperitoneal fluid. Further, CT can expedite the diagnosis of strangulation obstruction if findings including mesenteric edema, free peritoneal fluid, intestinal wall thickness, and the absence of fecalization of the small bowel content are present.

Early detection of bowel ischemia is paramount to successful surgical management of obstruction. Several studies have reported a diagnostic accuracy of greater than 90% with the use of CT in intestinal obstruction. Other work has attempted to identify radiographic characteristics that accurately detect ischemia. The presence of two or more beak signs, a whirl sign, a C- or U-shaped appearance of the bowel loop, and a high degree of obstruction were associated with nonsurgical treatment failure. Among studies utilizing IV contrast, reduced bowel wall enhancement had a 95% specificity in determining ischemia, and absence of mesenteric fluid had an 89% sensitivity in ruling out strangulation. O’Daly and colleagues found the association of peritoneal fluid with small bowel obstruction to be a strong predictor for the need for operative treatment. In settings where iodinated contrast is contraindicated, the finding of increased bowel-wall attenuation on unenhanced images is concerning for bowel ischemia, with a 100% specificity and 56% sensitivity.

Further reports evaluating the capability of CT to predict ischemia or strangulation have produced contradictory results. In a systematic review,
Mallo et al. found that the sensitivity, specificity, positive predictive value, and negative predictive value of CT for predicting ischemia were 83%, 92%, 79%, and 93%, respectively. Conversely, Sheedy et al. noted that with CT, sensitivity was 15% and specificity 94% for identifying bowel ischemia prospectively in patients with small bowel obstruction. A recent study by Zielinski et al. suggested that CT findings of free peritoneal fluid, thickened bowel, and mesenteric edema, combined with vomiting, were predictive of the need for eventual operative management, but though relatively sensitive for ischemia, CT was not very specific.

Some studies suggest that a CT scoring system may accurately predict the need for operative intervention. Jones et al. found that a scoring system with the criteria of a dilated small bowel, identification of a transition point, ascites, complete obstruction, partial obstruction, evidence of a closed-loop obstruction, and/or free air predicted the need for operative treatment in 75% of patients. It is important to remember that CT is better at identifying rather than excluding the presence of ischemia.

Although the increased use of CT in patients with bowel obstruction has provided greater diagnostic information, caution must be exercised in the use of this modality in distinguishing mechanical small bowel obstruction versus ileus. In one study, up to 20% of patients with a CT diagnosis of ileus required operative intervention eventually. Overall, the current preference for the use of CT is associated with an increased likelihood of operative intervention and decreased mortality; however, whether these associations are causal or coincidental remains unknown.

ULTRASONOGRAPHY

Ultrasonography (US) is used infrequently in the diagnosis of intestinal obstruction. Features concerning for strangulated bowel include akinetic bowel loops, hyperechoic and thickened mesentery, and presence of peritoneal fluid. Even though the reported specificity is 82%, sensitivity is 95%, and overall accuracy is 81%, this modality is highly operator-dependent, and the results are unlikely to be reproduced consistently in many institutions. US has been reported to be useful for the early recognition of strangulation obstruction in several Japanese and European studies; however, in the absence of an experienced ultrasonographer, the reliability of
US remains questionable. Furthermore, US is difficult to perform in obese patients, and extensive bowel gas may obscure the pattern of intestinal obstruction.

**MAGNETIC RESONANCE ENTEROGRAPHY**

Magnetic resonance enterography (MRE) has not been utilized as frequently as CT, because performance of this examination is more time consuming and requires substantial expertise in interpretation. In addition, in general practice MRE does not have a greater diagnostic accuracy than CT. In contrast, in centers that use MRE frequently, diagnostic accuracy exceeding 90% is achievable.\(^{64,65}\) MRE may have an advantage of distinguishing benign from malignant bowel strictures in patients with suspected malignant bowel obstruction.\(^{66}\)

**VIDEO CAPSULE ENDOSCOPY**

Video capsule endoscopy (VCE) may be a valuable diagnostic tool in patients with subacute or chronic intestinal obstruction where other imaging techniques have not revealed an etiology. VCE is particularly helpful in patients with obstruction related to a stricture caused by inflammation or malignancy.\(^{67}\) Overall, VCE may provide a diagnosis in nearly 40% of previously undiagnosed patients.\(^{68}\) A major concern with the use of VCE, however, is retention or impaction of the capsule either at a stricture or in any area of severe kinking related to adhesions in a patient who otherwise may have resolution of the obstruction without an operation. The incidence of this circumstance appears infrequent, but impaction may require celiotomy.

**Detection of Ischemia**

Identification of strangulation obstruction caused by ischemia of the intestine is a critical diagnosis, because the mortality associated with strangulated bowel obstruction is 9% to 40% compared to less than 5% in nonstrangulated intestinal obstruction.\(^{69}\) Unfortunately, clinical and imaging parameters claimed to permit early detection and operative intervention remain unreliable, and in fact do not lead to early diagnosis. As mentioned previously, studies examining the efficacy of CT for diagnosis of
strangulation obstruction have yielded mixed results in the determination of intestinal ischemia. Jancelewicz et al. found that decreased bowel wall enhancement on CT, leukocytosis, and peritoneal signs were the only independent predictors of strangulated obstruction on a multiple logistic regression analysis. Historically, acidosis, increased serum amylase activity, and increased serum lactate concentrations were also claimed to be indicators of strangulation. While abnormalities of these parameters may prove to be sensitive markers of strangulation, they generally lack specificity and do not offer useful positive or negative predictive value. Abdominal US and pulsed-Doppler US have been reported to be useful in identifying patients with strangulation. Ogata and associates reported that an akinetic, dilated loop of bowel observed on real-time US had a high sensitivity (90%) and specificity (93%) for the recognition of strangulation; the positive predictive value was 73%. The presence of free peritoneal fluid seen on US was also sensitive for strangulation. Given the conflicting evidence, the importance of integrating physical exam, imaging, and other clinical parameters (eg, worsening acidosis) when assessing a patient with bowel obstruction cannot be overemphasized.

**MANAGEMENT**

The initial management of patients with small bowel obstruction should focus on aggressive fluid resuscitation and nasogastric decompression of the stomach to prevent further accumulation of intestinal fluid and air. In addition, nasogastric decompression decreases the potential for aspiration and relieves vomiting. These therapies should be instituted in all patients, whether they are treated operatively or undergo a trial of nonoperative management. Blood should be analyzed for serum electrolyte concentrations, complete blood count, lactate concentration, typed and screened for potential transfusion, and when necessary, arterial blood gases should be analyzed as well.

The most important initial step in management is crystalloid fluid resuscitation that aims to replete fluid losses. Patients with small bowel obstruction often present with profound volume depletion and may require several liters of isotonic crystalloid solutions, such as normal saline (0.9% NaCl) or lactated Ringer solution with additional potassium as urine output is
restored. Resuscitation should be guided by urine output, provided the patient is hemodynamically stable and has normal renal function. Patients who are hemodynamically unstable or have impaired cardiac, pulmonary, or renal function may require monitoring of central venous pressure to better evaluate their volume status. Colloid solutions, such as 5% albumin or hetastarch, have little or no role in the resuscitation of patients with a small bowel obstruction. Proper fluid resuscitation includes correction of metabolic or electrolyte imbalances, which may be severe. Specifically, in patients who have experienced prolonged vomiting, potassium and chloride should be measured to diagnose hypokalemic, hypochloremic alkalosis and replacement therapy started after resuscitation with normal saline. Though potassium replacement is a critical component of therapy, replenishment of this electrolyte should begin only after renal function has been established by good urine output. Volume resuscitation, electrolyte replacement, and establishment of adequate urine output are critical before operative therapy is undertaken. Broad-spectrum antibiotics should be given to patients within an hour of the incision as prophylaxis against surgical site infection, but otherwise, antibiotics have no defined role postoperatively or in patients managed nonoperatively.

Most surgeons believe that nasogastric decompression is important to prevent further intestinal distention from swallowed air and to limit a broad transit of gastric contents. In addition, nasogastric decompression helps to prevent aspiration during vomiting and on induction of general anesthesia. Symptomatically, gastric decompression helps relieve abdominal distension and can improve respiratory function in patients with respiratory compromise.

Historically, long intestinal tubes placed distal to the pylorus were used to relieve small intestinal distention under the assumption that intestinal decompression may be therapeutic if related to adhesions, because the decompressed bowel may detort and thereby relieve the mechanical obstruction (Fig. 38-13). Success rates of up to 90% have been reported in some series of patients treated with a long nasointestinal tube. In contrast, however, most prospective and retrospective studies have failed to demonstrate the superiority of nasointestinal versus nasogastric intubation, making the added expense of fluoroscopic or endoscopic placement of a nasointestinal tube unwarranted. Use of these long intestinal tubes has fallen out of favor, and they are of historic interest only in the
preoperative treatment of small bowel obstruction.

**FIGURE 38-13** Abdominal radiograph showing distal passage of a long nasointestinal decompression tube into the small bowel distal to the ligament of Treitz.
Nonoperative Management

Nonoperative management of intestinal obstruction should be considered only in patients with uncomplicated intestinal obstruction in the absence of peritonitis, a progressive leukocytosis, or impaired bowel wall perfusion on imaging. When indicated, this approach is reported to be successful in 62% to 85% of patients.\(^73{-76}\) The rate of success of nonoperative management is influenced by patient selection, type of bowel obstruction (complete vs partial), etiology (eg, adhesions, hernia, or neoplasm), and the surgeon’s threshold for conversion to operative management. Patients successfully managed nonoperatively require fewer hospital days\(^73,74\) and avoid the morbidity or convalescence necessitated by an operation. Few studies have compared the long-term outcomes of patients with a small bowel obstruction treated nonoperatively versus operatively. One such study with over 4 years of follow-up reported by Landercasper and colleagues\(^77\) found a recurrence rate of 29% in patients managed operatively versus a recurrence rate of 53% for patients managed nonoperatively. Even though the recurrence rates may be greater with nonoperative management, the authors point out that about half of the patients managed nonoperatively never developed a recurrent small bowel obstruction.

A study by Rocha et al.\(^78\) used the radiologist definition of “high-grade” obstruction and reported that in these patients, comparing those treated conservatively versus those treated by operation, the conservatively treated patients had a significantly greater readmission rate at 5 years (24% vs 9%) than those treated operatively. Use of this radiologic finding may potentially extend the “indication” when criteria are met for high grade but not complete obstruction.

When patients with a small bowel obstruction are initially managed nonoperatively, vigilant attention must be paid to volume resuscitation, electrolyte homeostasis, and nasogastric decompression. Patients managed nonoperatively require the same aggressive resuscitation and replacement of daily losses with an appropriate crystalloid solution and electrolyte replacement as patients who are managed operatively. Fluid replacement should take into consideration the volume and electrolyte loss in the output of the nasogastric tube, urinary output, and insensible losses. Electrolytes should be monitored frequently and corrected as necessary. Delayed correction of
Adequate proximal decompression is important to allow the bowel an opportunity to decompress. This concept is accomplished by maintaining a functioning nasogastric tube. If the patient becomes progressively more distended or develops vomiting, tube placement should be evaluated and tube function confirmed by bedside evaluation. Standard nasogastric tubes should be inserted, such that the second of four marks is evident at the tip of the nares. The first mark is 40 cm from the tip of the tube—that is, the normal distance from the nares to the esophagogastric junction. Thus, if all four marks are outside the nares, the tube most likely is not in the stomach. Likewise, if no marks are visible, the tube is coiled within the stomach or is in the duodenum. On occasion, an abdominal radiograph is necessary to confirm placement. If the tube is noted on a radiograph to be out of position, it should be repositioned and imaged again for proper placement. On evaluation, the tube should be connected to the suction apparatus, sumping properly (if the tube has a sump port), and should be checked for patency by flushing and aspirating water through the suction lumen. Oral intake should be nil in the presence of a nasogastric tube. In addition, the tube should never be “clamped” for prolonged periods of time, because by traversing the esophagogastric junction, the tube will lead to an incompetent lower esophagogastric sphincter and potential aspiration. Connection of the tube to a drainage bag for a brief trial is an appropriate alternative to clamping and may be used as a test to determine patient readiness for nasogastric tube removal.

Absolute contraindications to nonoperative management include suspected ischemia, large bowel obstruction, closed-loop obstruction, acutely incarcerated or strangulated hernia, and perforation. In an attempt to define which patients with an uncomplicated small bowel obstruction can be successfully treated nonoperatively, Chen and colleagues used an orally administered, water-soluble contrast agent (Urografin) to study 116 patients with small bowel obstruction. The presence of contrast material within the colonic lumen within 8 hours of oral administration had an accuracy of 93% for predicting which patients would benefit from nonoperative therapy. In their study, only 19% of patients with a small bowel transit time of more than 8 hours had resolution of their obstruction with nonoperative treatment. One of the criteria for conversion to operative treatment was the failure of contrast
to reach the colon within 8 hours. Therefore, the 81% failure rate in patients in whom contrast never reached the colon within 8 hours after administration may be artificially high based on study design.

A relative contraindication to nonoperative management is complete small bowel obstruction—that is, dilated small intestine with no air in the bowel distally. In a prospective study by Fleshner and associates,\textsuperscript{74} all patients with an uncomplicated small bowel obstruction underwent an initial trial of nonoperative management. They were able to manage 45% of patients successfully with a complete obstruction (by their definition), while 66% of patients with a partial obstruction were successfully managed nonoperatively, all with no mortality. These investigators, however, did not describe the incidence of intestinal ischemia at operation based on the presence or absence of complete versus partial obstruction. Another study by Fevang and colleagues\textsuperscript{73} reported a 42% success rate in managing patients with a complete small bowel obstruction nonoperatively. When they compared complete and partial obstructions managed nonoperatively, there was a greater rate of bowel strangulation (10% vs 4%) and need for resection (14% vs 8%) in the group with complete obstruction at the time of operation for treatment failure. This group noted a mortality of 6% in patients with a complete obstruction initially managed nonoperatively versus 0% mortality for patients with a partial obstruction initially managed nonoperatively. Other groups have also noted a greater rate of ischemic bowel coupled with a lesser success rate in those patients with a complete obstruction managed nonoperatively.\textsuperscript{72,78} These studies and the unreliability of clinical acumen to recognize strangulation obstruction accurately have led many surgeons to favor early operation for all patients with a complete small bowel obstruction,\textsuperscript{76} leading to the often-quoted phrase “The sun should never rise or set on a (complete) small bowel obstruction.”

To better delineate partial and complete obstruction, studies have adopted a protocol-driven approach to utilize water-soluble contrast agents (WSCA) in nonoperative management. Among the protocols described in the literature, patients presenting with signs and symptoms of small bowel obstruction were assessed clinically and on CT imaging. Those demonstrating features concerning for ischemia underwent operative exploration immediately following appropriate resuscitation. The remaining patients receiving nonoperative treatment underwent gastric decompression, fluid resuscitation, urinary catheter placement, and WSCA administration.
Following WSCA, abdominal plain films were taken at 8 hours\textsuperscript{80,81} after WSCA or 1, 2, 4, and 8 hours\textsuperscript{82} after administration, depending on the study. Patients passed WSCA challenge if contrast reached the right colon by times ranging from 8 hours\textsuperscript{80,81} to 24 hours\textsuperscript{82} after WSCA. Patients who developed worsening signs and symptoms consistent with peritonitis underwent exploratory laparotomy. Among the patients who failed WSCA challenge but did not have a worsening exam, time from WSCA administration to operative management varied from 24 hours\textsuperscript{82} to 4 to 5 days.\textsuperscript{80}

Success rates using WSCA protocols have ranged from 57\%\textsuperscript{82} to 90.5\%.\textsuperscript{83} Based on a recent meta-analysis of 14 prospective trials, presence of contrast in the colon predicted resolution of obstruction with 96\% sensitivity, 98\% specificity, 99\% positive predictive value, and 90\% negative predictive value. The authors supported use of WSCA as both a diagnostic and therapeutic tool and demonstrated a decreased need for surgery and decreased hospital length of stay,\textsuperscript{52} although results from individual studies remain mixed regarding length of stay and frequency of laparotomy. These studies support use of WSCA protocols in adhesive small bowel obstruction and suggest that protocols decrease use of non-therapeutic laparotomies while diminishing delays in surgical care when indicated (Fig. 38-14).
If nonoperative management is attempted in a patient with complete obstruction, the decision should be made with the understanding that there is a definite risk of overlooking an underlying strangulation obstruction, and thus there should be a low threshold for operative intervention in patients with complete obstruction.

When to Convert to Operative Management

Prompt operative intervention is mandatory in patients who develop signs and symptoms suggestive of a strangulation obstruction. These parameters include fever, tachycardia, leukocytosis, localized tenderness, continuous abdominal pain, and peritonitis. The presence of any three of these signs has an 82% predictive value for strangulation obstruction. Similarly, the presence of any four of the above signs has a near 100% predictive value for strangulation obstruction. Obviously, patients who develop free air, signs of a closed-loop obstruction on abdominal radiograph, or gross peritonitis require...
emergent operative exploration. If CT demonstrates evidence of ischemia, such as pneumatosis intestinalis, bowel wall thickening, portal venous gas, generalized ascites, or nonenhancement of the bowel wall, operative intervention should be strongly considered.\textsuperscript{76}

The timing of conversion to operative management in a patient with a small bowel obstruction who is not improving with nonoperative management is more controversial. Some surgeons advocate operative intervention in any patient who fails to show improvement within 48 hours of initiating therapy.\textsuperscript{72,75} Others advocate a more liberal use of nonoperative therapy, citing a mean time to successful resolution of up to 4.6 days.\textsuperscript{74} The authors believe that nonoperative management can be continued greater than 48 hours with the understanding that delaying inevitable operative treatment will result in a greater overall hospital stay and increased costs, and may place the patient at increased risk for perioperative morbidity. As mentioned earlier, implementation of a protocol-driven approach with use of water-soluble contrast agents may be of diagnostic benefit in this setting, though further studies are needed to identify the optimal time to pursue operative care. It is important for the surgeon to remember that nonoperative management always carries a calculated risk of overlooking an underlying strangulation obstruction.\textsuperscript{85}

**Operative Management**

Once the decision has been made to pursue operative management, steps should be taken to prevent peri- and postoperative complications. Preoperative preparation includes assessing the medical fitness of the patient, and as time allows, taking steps to optimize the patient’s medical status. Special consideration should be given to ensure that the patient has been resuscitated adequately by establishing adequate urine output, appropriate antibiotics have been administered, and any electrolyte abnormalities have been addressed. Consideration should be given to the administration of β-blockers to patients with cardiovascular comorbidities and especially to those who were on β-blockers prior to admission.\textsuperscript{85} A nasogastric tube should already be in place to decrease the risk of aspiration during the induction of anesthesia; nevertheless, a rapid-sequence anesthetic induction will be necessary to protect the airway during intubation, even in the presence of a
Several decisions must be made with regard to operative planning to provide the safest approach that will afford the best outcome for each individual patient. The choice of operative approach and incision is important to allow the surgeon adequate exposure and visibility. A laparoscopic approach should be considered in some patients. When an obstruction develops in the early postoperative period, the original incision should be reopened provided extensive adhesions were not present originally. Safe entrance into the peritoneal cavity may be best achieved by approaching this from the extremes of the previous incision rather than going directly through the mid-portion of the incision. In patients without a history of prior abdominal operation or those who are remote from their original operation, a midline celiotomy affords the best exposure to all four quadrants of the abdomen. For example, patients with upper oblique, transverse, or subcostal type incisions may have pelvic adhesions that are difficult to address from the upper abdomen, especially through a high transverse incision.

Once within the abdominal cavity, the first step is to identify the site and cause of obstruction. If the point of obstruction is not obvious, decompressed bowel distal to the obstruction can be identified and followed proximally to the point of obstruction. Care should be taken when handling the obstructed bowel at or near the point of obstruction when acutely obstructed, especially if it is fixed at an apparent site of obstruction or if it is ischemic. This region is at high risk for strangulation and infarction, making it more likely to rupture with spillage of bacteria-laden enteric contents into the abdomen. The dilated bowel proximal to the offending obstruction is often thin-walled and at increased risk for perforation if the obstruction is acute. After the offending obstruction has been corrected, a thorough exploration of all four quadrants should always be undertaken to ensure that all intestinal injuries are repaired, nonviable segments are resected, and a second site of obstruction or fixation is not overlooked. This concept is especially true for volvulated segments of small bowel where two points of fixation are often present. Occasionally, obstructing bands traversing a sizeable part of the peritoneum can affect more than one loop of bowel. When a small bowel resection is necessary, intestinal continuity of the small bowel can be accomplished generally with a primary anastomosis unless there is generalized peritonitis and the edges of the remnant bowel are of questionable viability. When an intestinal anastomosis is performed, the surgeon must assess the discrepancy in bowel diameter and
wall thickness between the obstructed proximal bowel and decompressed distal bowel when choosing anastomotic techniques. The surgeon may consider a side-to-side or end-to-side anastomosis in situations where massive dilation of the proximal bowel makes an end-to-end anastomosis difficult technically. In addition, a stapled anastomosis may be less safe in cases where a large discrepancy in bowel wall thickness exists or when there is bowel wall edema, because uniform approximation of the tissue for a given staple height may not be possible.

Abdominal closure may be difficult to achieve when the small bowel is massively dilated. In these cases, intraoperative intestinal decompression will facilitate closure. Techniques described for intraoperative decompression include manual retrograde decompression into the stomach (with careful handling of the obstructed bowel), intraoperative passage of a long nasointestinal tube and, rarely, performance of a controlled enterotomy with passage of a decompressing tube. The latter technique is strongly discouraged except under very select circumstances, such as tremendous intestinal distention preventing abdominal closure or distention threatening bowel viability. Manual retrograde decompression of luminal contents around the ligament of Treitz, through the pylorus, and into the stomach allows for aspiration through the nasogastric tube by the anesthetist. This maneuver is the safest and quickest technique because it allows closure of the abdominal wall while avoiding an enterotomy and excessive manipulation of the bowel. When decompressing the bowel, the inflamed and distended bowel must be handled gently, because experimental studies have demonstrated an increased rate of bacteremia after extensive manipulation of obstructed bowel. In addition, the anesthesia team should be alerted to the maneuver to be certain that their nasogastric tube is functioning well. Although intraoperative decompression has not been shown to decrease the rate of postoperative complications or the speed of return of bowel function, it certainly does make abdominal closure easier, faster, and safer.

Nonviable bowel needs to be identified and resected. Resection should be undertaken with caution, especially in patients with a limited length of bowel from a previous resection or those with large sections of ischemia. Adjuncts for determining bowel viability include the use of Doppler US and intravenous fluorescein. These tests are relatively subjective, should be used with caution, and are only adjuncts to sound clinical judgment. In patients who would otherwise be left with less than two-thirds of their original bowel
length after resection of all bowel of questionable ischemia, consideration
may be given to resecting all the grossly necrotic or obviously nonviable
bowel but preserving bowel of questionable viability and performing an end
ostomy or a second-look procedure 12 to 24 hours later, particularly if the
viability of the ends to be anastomosed is in question.

**BYPASS VERSUS RESECTION**

In patients with an incurable malignant small bowel obstruction, if the
offending obstruction is unable to be released or it is deemed unsafe to
attempt to dissect out the site of obstruction, intestinal bypass can be
performed. Bypass relieves the obstruction while reestablishing intestinal
continuity and preventing a closed-loop obstruction; however, the
advisability of a bypass procedure should be considered. For instance, in the
presence of carcinomatosis, a bypass may prove fastest and safest, because
patient survival will be short. In contrast, patients with certain chronic
inflammatory diseases will remain at risk for ongoing problems (eg, Crohn’s
disease or tuberculosis) related to the inflammation in any “bypassed”
segment, and therefore such patients may be served better by resection than
simple bypass.

The surgeon should at least consider an initial laparoscopic, minimal
access approach in patients with uncomplicated small bowel obstruction.
Laparoscopy is known to cause fewer adhesions than open laparotomy\(^89\) and
in that regard may be superior to laparotomy for the treatment of adhesive
small bowel obstruction. Several studies have shown laparoscopy to be a safe
and effective means of access for the operative treatment of small bowel
obstruction.\(^86,90–92\) When successful, a laparoscopic approach decreases both
the duration of hospital stay\(^86,90–92\) and the complication rate.\(^90,92\) Patients
successfully treated laparoscopically appear to have more rapid return of
bowel function.\(^90,92\) These reports show a large benefit to laparoscopic
treatment for small bowel obstruction, but need to be interpreted carefully.
Many series compare patients treated laparoscopically to those who failed
initial laparoscopic treatment. Those patients unable to be treated
laparoscopically likely had more extensive adhesions or complicated
pathology possibly requiring resection. Operative intervention in these
patients would be more involved and complex whether done open or
laparoscopically. One would expect these patients to have greater hospital
stays, greater complication rates, and slower return of bowel function independent of the method of abdominal access. In addition, the skill and confidence level of the surgeon should weigh in the decision to approach the obstruction laparoscopically. First, if the surgeon lacks skill in using moderately advanced laparoscopic techniques, an open operation may be a better choice. Similarly, if the patient is known to have a frozen abdomen or has either a severely distended, tense abdomen with markedly distended bowel or multiple dense adhesions at the time of insertion of the laparoscope, conversion to an open procedure is wise. Initial access for creating the pneumoperitoneum in a patient with a small bowel obstruction is achieved best by a fully open approach under total visual control, but limited data support this concept.

RECURRENT SMALL BOWEL OBSTRUCTION

Although the results of individual studies vary, between 4% and 34% of patients will experience recurrent small bowel obstruction regardless of management modality.9,74,76,77,79,92 This wide range of recurrence rates likely results from variations in both the duration and quality of follow-up between studies as well as the etiology of the original bowel obstruction. Recurrent obstruction is more common in patients with multiple adhesions, matted adhesions, previous admissions for small bowel obstruction, and previous pelvic, colonic, and rectal surgery.9,77

In the past, numerous attempts have been made by surgeons to control the formation of adhesions in an effort to prevent future mechanical obstruction. A simple technique to prevent adherence of the bowel to the undersurface of the fascial incision is to interpose the omentum between the bowel and the incision. Theoretically, when adhesions from the posterior surface of the anterior abdominal wall form after omental interposition, they will involve the omentum and not the underlying bowel. Other more intricate techniques, such as the Noble plication and the Childs−Phillips transmesenteric plication, have been described in the more distant past. These procedures involve the suturing adjacent loops of small bowel into an orderly pattern in an attempt to plicate the bowel permanently in a position that will not allow mechanical obstruction. Although initial reports were encouraging, the Noble and Childs−Phillips procedures have multiple complications and are of historic interest only. The problems associated with plication procedures have included
prolonged operative times and high rates of enterocutaneous and enteroenteric fistula, abdominal abscess, and wound infection; moreover, the rate of recurrent obstruction is as great as 19%, bringing into question their efficacy. Attempts to “plicate” the bowel with a long intestinal tube, so-called intraluminal plication, have not proved effective.

In some patients, complete or adequate adhesiolysis is not possible or may risk vascular injury to a substantial segment of bowel because of the acute inflammatory nature or tenacity of the adhesions. This situation is especially common when celiotomy is deemed necessary or performed too soon after a previous intra-abdominal procedure (see the following section on early postoperative small bowel obstruction). This situation is especially common when the previous operation involved an extensive adhesiolysis. In such situations, it may be important to control any bowel injuries present, end any further dissection, and conclude the operation to prevent further bowel injury and its potential sequelae. This “conservative” approach may allow the acute inflammatory process to resolve or regress (often 3-6 months); should the obstruction not resolve by 6 months, the plan should be to reoperate at a time when the adhesions have matured, allowing a more controllable and much safer adhesiolysis. In some situations, the mature decision might be to provide proximal diversion with a proximal enterostomy if the obstruction has no chance for resolution (eg, due to malignancy or radiation) or if a more distal bowel repair is tenuous, or to place a tube gastrostomy for diversion and patient comfort. Pursuing a futile attempt to complete the adhesiolysis puts the patient at risk for serious bowel injury or devascularization injury necessitating resection of otherwise normal bowel with the risk of enterocutaneous fistula or subsequent short bowel syndrome.

ADHESION PREVENTION

Over the last 100 years, multiple approaches have been employed in an attempt to prevent the formation of unwanted postoperative adhesions. These attempts include, among others, the use of cow cecum, shark peritoneum, sea snake venom, and fish bladder, as well as multiple fluids, mechanical barriers, and gels.93 The concept of separating injured surfaces mechanically to prevent adhesions is attractive. The formation of fibrin bridges (and thus adhesions) may be preventable by separating injured surfaces in the postoperative interval during the critical period of healing and
mesothelialization by application of an absorbable biofilm. Estimates of the minimum amount of time necessary for an impermeable or semipermeable barrier to prevent adhesion formation appear to be about 36 hours. Some authors have placed a Silastic sheet between two injured peritoneal surfaces and when left in place for 36 hours, no adhesions formed between these surfaces thereafter.²² Others have postulated that separating the surfaces at risk for the first 5 to 7 days until full mesothelialization occurs would seem to be most effective; however, the barrier should not incite its own inflammatory response and should not decrease fibrinolytic activity or suppress access to oxygen. The ideal product, therefore, should be bioabsorbable, last only 5 to 7 days, be easy to apply, be interposed between all injured surfaces, and not itself incite an inflammatory reaction.

The most effective method to date has been the application of a sheet of bioresorbable hyaluronate membrane. This approach has been shown to decrease the formation of adhesions at the site of application.⁹³,⁹⁴ Multiple reviews have supported that use of this product decreased adhesion formation.⁹⁵–⁹⁸ Whether hyaluronate application resulted in decreased incidence of reoperation for adhesive small bowel obstruction remains unclear. Reviews by Kumar and Zeng showed no association between hyaluronate use and incidence of postoperative bowel obstruction nor did hyaluronate decrease the need for operative intervention for intestinal obstruction.⁹⁶,⁹⁷ Furthermore, if the membrane is wrapped around an intestinal anastomosis, the leak rate is increased. In a study evaluating long-term follow-up of barrier use, van der Wal and colleagues report no decrease in frequency of bowel obstruction, and barrier use failed to improve quality of life as determined on patient survey.⁹⁹

Initial concerns that were raised over the safety of hyaluronate barriers appear unfounded, with the exception of iron cross-lined hyaluronate that was withdrawn from the market. A prospective, randomized, controlled trial showed that hyaluronate barriers did not increase the risk of intra-abdominal abscess or pulmonary embolism⁹⁵; however, in a post-hoc subgroup analysis of 289 patients in whom the hyaluronate membrane was wrapped around a fresh anastomosis, the rates of leak, fistula formation, peritonitis, abscess, and sepsis were increased. Based on these studies and assumptions, the use of hyaluronate membranes in elective abdominal surgery does decrease the amount of postoperative adhesions at the site of application but does not
decrease the incidence of intestinal obstruction or the need for future reoperation for obstruction. Use of these products requires careful consideration, because they are expensive and their clinical benefit appears to be relatively low.

Other materials or substances are being developed that may someday move to the forefront of adhesion prevention. These include gel and liquid preparations such as hyaluronic acid and carboxymethylcellulose, hydrogel, fibrin sealant, and protein polymers. Other adhesion barriers include oxidized regenerated cellulose (ORC). ORC has been well studied and does help prevent adhesion formation, but its use requires a blood-free field that at times is not practical to achieve. The use of ORC, like hyaluronate membranes, has not been shown to decrease the incidence of subsequent adhesive small bowel obstruction.\textsuperscript{101} Strategies including use of postoperative hyperbaric oxygen, peritoneal cell transplantation, and use of fetal-liver mesothelial cells have been described in animal models but have yet to be applied in a clinical setting.\textsuperscript{102,103}

**EARLY POSTOPERATIVE SMALL BOWEL OBSTRUCTION**

Early postoperative small bowel obstruction, herein defined as within 6 weeks of the original operation, is a relatively uncommon problem but remains a real dilemma encountered in every practice performing abdominal operations.

It is often difficult, if not impossible, to distinguish early obstruction from postoperative ileus, but fortunately the management is usually quite similar. Patients with suspected early mechanical small bowel obstruction should be managed initially by nasogastric decompression, fluid resuscitation, and correction of any electrolyte abnormalities. After a thorough physical examination and the decision that emergent intervention is not indicated, a search for the cause of obstruction should be undertaken. CT can be helpful in determining the etiology of an obstruction but is notoriously unreliable at differentiating ileus versus partial obstruction. Obstructions caused by extrinsic bowel compression amenable to percutaneous correction, including fluid collections, abscesses, and hematomas, may be diagnosed and treated by percutaneous drainage. CT may be able to detect those causes of obstruction that will likely require operative intervention, such as internal hernia, fascial
dehiscence, and uncontrolled anastomotic leak. Early CT may be warranted in patients who had a laparoscopic operation and have signs of early obstruction, because a port site hernia may be evident and would require prompt operation.

Generally, two categories of patients with early postoperative small bowel obstruction have been recognized. The first category includes those in whom the obstruction becomes evident within 10 days of an abdominal operation. Conservative management is advised usually as long as signs and symptoms of ischemia and strangulation obstruction are not present and other remediable causes have been excluded. Patients within this time frame are not at a substantially increased risk of bowel-related complications after celiotomy, provided there are no internal hernias and, if the original operation was done laparoscopically, that port site hernias can be excluded. It is important to rule out correctable causes of extrinsic compression and reverse any electrolyte abnormalities, especially if ileus is also suspected. Strangulation obstruction, albeit rare, can occur in this group of patients, and thus a high index of suspicion must always be maintained. The etiology of a strangulation obstruction in this group is almost never related to adhesions but rather to some surgical misadventure, such as internal hernia, an overlooked segment of ischemia at the original celiotomy, bowel entrapped in the fascial closure, or an unsuspected abdominal wall hernia.

The second category of patients is those presenting between 10 days and 6 weeks after operation. Conservative management is advised whenever possible for patients in this category as well. The risk of iatrogenic bowel complications during and after reoperation so early after celiotomy increases dramatically in this group secondary to the dense adhesions often present during this period after abdominal operation. The time period from 7 to 10 days up until 6 to 12 weeks postoperatively represents the window when the greatest inflammatory reaction is present intraperitoneally. The developing adhesions are highly vascular and friable. If the patient had no or very minimal adhesions at the time of celiotomy, reoperation is warranted; however, in a small, unpredictable group of patients without any previous adhesions, and reliably so in those with dense adhesions that had required substantial adhesiolysis at the time of original celiotomy, an acute inflammatory reaction involving the peritoneal surfaces may agglutinate adjacent loops of bowel, often involving the omentum and mesenteric surfaces.
Operations performed during this period have a much greater rate of iatrogenic injury and subsequent fistula formation. Those patients not responding to conservative management during this period are best placed on parenteral nutrition until the obstruction resolves or they are more than 6 to 12 weeks out from their last celiotomy. At this time, the decision to reoperate is made based on several considerations. First, if the patient had relatively few adhesions at the time of celiotomy, reexploration at 6 weeks to 3 months postoperatively may be warranted. In contrast, in those patients who required an extensive adhesiolysis at the time of original celiotomy, many experienced surgeons wait for a full 6 months prior to reoperation for several reasons: (1) by 6 months, the adhesions are reliably less vascular and more mature; (2) reoperation prior to 3 months may reveal a frozen abdomen in which the obstruction may be unable to be dissected free safely; and (3) the obstruction may resolve as the adhesions mature.

**BOWEL OBSTRUCTION AFTER ROUX-EN-Y GASTRIC BYPASS SURGERY**

As with all other operations and maybe more so in the current era of laparoscopic Roux-en-Y gastric bypass (RYGB), bowel obstruction is a worrisome complication after bariatric surgery for morbid obesity. Estimates of the rate of bowel obstruction after RYGB vary within a reported range of 0.3% to greater than 9% depending on the technique used to perform the operation. The rate of bowel obstruction appears to be less after open RYGB, but there are no large prospective studies comparing laparoscopic to open procedures at this time. In a large, collected review of more than 9500 patients undergoing laparoscopic RYGB, the rate of bowel obstruction was 3.6%. Although some controversy exists, most authors suggest that the rate of bowel obstruction is less with use of an antecolic versus a retrocolic orientation of the Roux limb for the gastric bypass. Bowel obstruction after RYGB can occur secondary to a variety of etiologies; however, the four most common etiologies, in decreasing order of frequency, are internal hernia, adhesive obstruction, stenosis at the jejunojejunostomy, and incisional hernia.

The diagnosis of bowel obstruction after laparoscopic RYGB is more difficult than after other surgical procedures secondary to the altered gastrointestinal anatomy created by the procedure and the often less typical
response of the patient with morbid obesity. After RYGB, the symptoms of bowel obstruction can be vague, and because the most common etiology is internal hernia, the symptoms are often intermittent. Abdominal pain is the most common symptom present in 82% of patients in one large series, and importantly, nausea and vomiting were seen in fewer than 50% of patients in this series. All three symptoms were present in only 28% of patients. Unfortunately, imaging studies also have a lesser sensitivity for bowel obstruction in patients after RYGB, with reported sensitivities of 51%, 57%, and 33% for CT, UGI contrast study, and plain abdominal radiography, respectively. When patients with unexpected gastrointestinal symptoms after RYGB are assessed, a high index of suspicion for bowel obstruction is warranted. Given the frequency of internal hernia as a cause of postoperative bowel obstruction and the low sensitivity of radiologic evaluation for bowel obstruction in patients after RYGB, a low threshold for laparoscopic exploration is warranted in patients with suspected bowel obstruction.

Internal hernia is the most common cause of bowel obstruction after RYGB. Anatomically, there are three different types of internal hernias seen after RYGB. All three types of internal hernias are transmesenteric defects created during the formation of the Roux limb and are illustrated in Fig. 38-3. The so-called Peterson hernia occurs in the infracolic compartment through the potential space between the mesentery of the Roux limb, the transverse mesocolon, and the retroperitoneum, and can be seen with either an antecolic or retrocolic Roux limb. Herniation through the mesenteric defect created by the jejunojejunostomy is the second site of internal hernia observed after RYGB and can occur with both antecolic and retrocolic gastric bypass. Herniation through the mesenteric defect in the transverse mesocolon created by passage of the retrocolic Roux limb is the third type of internal hernia observed in RYGB and is only seen in retrocolic gastric bypass; this type of internal hernia was the most common type before the importance of meticulous closure of this defect was appreciated. Most authors believe that bowel obstruction after RYGB is substantially more common after laparoscopic retrocolic bypass, with reported rates of 3.2% to 5.1% after retrocolic and 0.3% to 1.7% after antecolic bypass reported in the largest series. Meticulous closure of all potential hernia spaces with nonabsorbable suture at the time of RYGB is the best way to prevent internal hernia; however, care must be taken when closing the mesocolic defect, because obstruction at the mesocolic window from tight scar formation has
also been reported as a cause of bowel obstruction after RYGB. When operating on a patient with internal hernia after RYGB, careful closure of the hernia defect with nonabsorbable suture after reduction in the hernia is the treatment of choice.

**RADIATION ENTEROPATHY**

The management of radiation enteropathy is often difficult and frustrating. The clinical presentation can be quite diverse with recurrent intermittent small bowel obstruction, a true, chronic, persistent partial small bowel obstruction, or chronic diarrhea/malabsorption. Operative management is often extremely challenging secondary to the dense adhesions and chronic inflammatory reaction present after radiation. These patients also tend to develop recurrent areas of enteropathy consistent with progression of disease in bowel that appeared normal previously, because this ischemic disease is an ongoing and progressive chronic process. The need for operative correction with a resection and anastomosis has been reported to have a mortality rate as high as 21% in some series. Patients with radiation enteropathy also have a high rate of anastomotic leak and fistula formation after operation because of the compromised vascular supply to the bowel. These effects are magnified in patients with atherosclerosis, hyperlipidemia, or type 2 diabetes. For these reasons, a cautious, conservative approach to the patient with radiation enteropathy is warranted whenever possible.

When operative management is necessary, the surgeon must decide between resection, bypass of the affected segment, or adhesiolysis. As noted earlier, resection has been reported to have a high mortality rate, with a 36% incidence of leak after primary anastomosis. In the same study, bypass of the affected segment had a 10% mortality and 6% leak rate. Surgeons advocating aggressive resection back to healthy bowel, however, have reported leak rates between 0% and 8% when confounding conditions (abscess, fistula, necrosis, or recurrent cancer) were absent; such an aggressive approach may require an extensive resection but often involves resection of nonfunctional bowel anyway. In their retrospective analysis, Li et al. identified American Society of Anesthesiologists (ASA) class of III to IV, intraoperative transfusion, preoperative anemia, thrombocytopenia, and presence of radiation uropathy as independent risk factors to Clavien–Dindo grade III to IV morbidity when ileal or ileocecal resection was undertaken.
Given the complexities in managing radiation enteropathy, implementation of a scoring system may help direct care and improve outcomes. Short bowel syndrome is always a concern, especially because the involved bowel is usually the distal ileum.

Most surgeons approach the treatment of radiation enteropathy cautiously. In those patients with recurrent cancer and radiation enteropathy, treatment should consist of palliative bypass of the diseased segment with creation of an anastomosis in visibly normal tissue. If the obstructive process is localized, wide resection back to healthy, non-irradiated tissue (if possible) with primary anastomosis is acceptable, provided adequate absorptive area is preserved. Usually this involves anastomosis from small bowel to the ascending colon, because the terminal ileum has usually been within the radiation field. While ideally a complete resection of the entire involved small bowel is optimal, the surgeon must consider the extent of the resection necessary as well as the anatomic segment involved. Because the distal ileum is commonly involved, major resection back to reliably normal, non-irradiated small bowel may require a total or subtotal ileal resection that carries its own nutritional complications. Thus, the surgeon is faced with a decision concerning preservation of mildly involved but functional ileum versus complete resection. In contrast, if the bowel is severely involved and nonfunctional, resection, despite its side effects, may be the best option. When the affected area contains dense adhesions or is stuck deep within the pelvis, bypass may be a better choice to avoid the very real concern of potential iatrogenic injury to the bowel, bladder, pelvic organs, and ureters; however, if there is a localized abscess or associated septic process, bypass is not a good option because the ischemic inflammatory process will continue. Attempts at complete lysis of adhesions alone without resection are controversial due to the risk of traumatizing the intestine with potential fistula formation. For the patient with advanced disease who presents years after irradiation, adhesiolysis may not be a good option, especially if the bowel is matted and agglutinated. In contrast, in the case of isolated adhesive bands and the patient being early (<2 years) after irradiation, lysis alone may be warranted; much of the decision needs to be based on the quality of the involved bowel and the site of obstruction. If the bowel is thickened, nonpliable, and strictured, resection or bypass is best.

CARCINOMATOSIS AND MALIGNANT OBSTRUCTION
Bowel obstruction in the setting of carcinomatosis often represents the terminal phase of the malignant disease. Operative management is entirely palliative and needs to be applied selectively. In the case of limited life expectancy and malignant cachexia or ascites, nonoperative palliative measures are advised because operative intervention would be unnecessary and associated with a poor quality of life due to the convalescence required after a non-curative celiotomy. However, some patients with a good performance status may have a long life expectancy, and in this case, operative bypass with the idea of permitting renewed oral intake may be indicated. Patients and their families should be counseled that the relief of their obstruction will not affect disease progression but may improve quality of life. In addition, the surgeon should keep in mind that up to one-third of bowel obstructions presenting in the setting of carcinomatosis are due to adhesions and not to malignant obstruction. Therefore, a short trial of conservative therapy with rehydration and nasogastric decompression is usually advisable, although many patients with carcinomatosis will fail this intervention. In addition, depending on the location and extent of the malignant disease involving the gastrointestinal tract, a palliative endoscopic stent placement may relieve the obstruction (Fig. 38-15).

**FIGURE 38-15**  
expanding metal stents, Surgery 2005;Jan;137(1):42–47.)

An initial minimal access, laparoscopic approach should at least be entertained in patients with a malignant obstruction, provided the access to the peritoneal cavity is safe. The least invasive approach is best for these patients, and if palliation, such as a bypass or gastrostomy tube, can be achieved laparoscopically, the patient would benefit substantially with decreased pain, possibly a shorter convalescence, and decreased duration of hospital stay, all of which are important considerations in the palliative care of patients with a limited life expectancy.

At exploration, multiple scenarios may be encountered. Some patients will have an isolated area of adhesions and require only adhesiolysis. Others will have a solitary metastasis causing either an intra- or extraluminal obstruction that can be corrected with a limited resection or bypass. If multiple areas of adhesions are present or the affected area is adherent to the abdominal wall or intra-abdominal structures in the patients with incurable malignant obstruction, bypass of the involved segment will provide symptom relief and the fewest opportunities for complication. One should consider placement of a tube gastrostomy if there is any question of the success of the operation, if impending obstruction seems imminent, or if relief of the obstruction is not possible. In the event of recurrent obstruction, a tube gastrostomy can be used to decompress the stomach and avoid the discomfort associated with a nasogastric tube. The decision to place a palliative, decompressive, tube gastrostomy is more difficult in the presence of ascites. In this situation, a better option would be a tube pharyngostomy. In addition, if histologic diagnosis of the neoplasm had been obtained previously, a repeat biopsy should be entertained to ensure that the neoplasm has histologic characteristics consistent with the original biopsy.

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TUMORS OF THE SMALL INTESTINE

Michael M. Reader • Barbara Lee Bass

Primary tumors of the small intestine, both benign and malignant, are rare. With the potential to arise from virtually every cell type within the small intestine—the epithelium, neural tissues, and lymphatic and mesenchymal cells—the small bowel may also be the site for metastases from other primary tumors. The variety and uncommon nature of these tumors make generalizations regarding their management difficult. In this chapter, we will review the epidemiology and clinical diagnostic and management strategies for benign and malignant neoplasms of the small bowel.

EPIDEMIOLOGY

Although the small bowel accounts for 75% of the length and 90% of the mucosal surface area of the gastrointestinal tract, less than 2% to 5% of gastrointestinal malignancies arise in this organ. Most of these tumors are clinically silent. Autopsy series have identified incidental small bowel tumors in 0.2% to 0.3% of hospital deaths—a rate 15 times the operative incidence of small bowel resections for tumors.\textsuperscript{1,2} Over the past few decades, the overall incidence of small bowel tumors has increased, likely due to
enhanced detection with new diagnostic modalities. Although the incidence of adenocarcinoma has remained stable, there has been an almost 4-fold increase in the incidence of small intestinal neuroendocrine tumors (SI-NETs), which are now the most common primary tumor of the small bowel.\textsuperscript{1,2}

Given the rare nature of these tumors, most published reports are collections of relatively small series of tumors accrued over a period of many years. Interestingly, these reports differ regarding the type of small bowel tumor, the distribution of tumors, and until the advent of molecular diagnostic criteria for gastrointestinal stromal tumors (GISTs), the classification of tumors of stromal origin. Nonetheless, in most series, adenocarcinomas (30\%-50\%), GISTs (15\%), SI-NETs (carcinoid tumors; 20\%-30\%), and lymphomas (15\%) compose the most common malignant tumors.\textsuperscript{2,3} Small bowel tumors are more prevalent in older patients, with over 65\% of patients with small bowel adenocarcinoma being age 60 or older.\textsuperscript{3} The proportion of small bowel tumors that are benign varies from 14\% to 52\% in different series, a disparity explained by the failure to detect these typically asymptomatic benign lesions.

There are no satisfactory explanations for the observed variation in prevalence of small bowel tumors around the world. Neuroendocrine tumors (NETs) are uncommon in Asian series, whereas GISTs compose a higher proportion of reported series in the East.\textsuperscript{4,5} Men are slightly more likely to develop small bowel neoplasms than women, with a male preponderance reported for both benign and malignant tumors.

**PATHOGENESIS**

Given the length of the small bowel and its large mucosal surface, it is intriguing that it is such an uncommon site for malignancy. Unlike the adenoma-carcinoma sequence seen in the colon, a clear molecular progression sequence has not been defined in the small bowel other than the known polyposis syndromes. Only perianal neoplastic adenomas are known to be premalignant lesions with the potential to progress to adenocarcinomas. Adenomatous polyps arising anywhere in the small bowel presumably have similar potential for malignant transformation, although the molecular traits of this transformation remain unknown. Such progression has not been
definitively documented at other sites in the small bowel. The only small bowel primary tumor with a known genetic pathogenesis is the GIST, which is linked to deleterious mutations of the KIT and PDGFRA genes.

Based on theories of luminal injury defined in the colonic mucosa, several hypotheses are proposed regarding the pathogenesis of epithelial-derived small bowel tumors. Unlike the colon with its high bacterial luminal content, the lumen of the healthy small bowel is relatively sparsely colonized with a commensal microbiome; bacterial metabolites implicated in the genetic alterations of colon carcinogenesis are absent. Transit through the small bowel is rapid—30 minutes to 2 hours—so exposure to potential toxins and metabolites is much more limited. The alkaline, mucus-rich succus entericus of the small bowel may have protective capacity and less noxious potential than the more solid contents of the colon. Enterocytes of the brush border epithelium express the enzyme benzopyrene hydroxylase, possibly protecting against mucosal damage by detoxifying the carcinogen benzopyrene. And lastly, high levels of luminal IgA and greater distribution of lymphoid tissue in the small intestinal epithelium and submucosa may provide an additional protective mechanism via an immune surveillance mechanism.

Bile acids and their metabolites have been implicated in the pathogenesis of small bowel adenocarcinoma. Postcholecystectomy patients may be at greater risk for the development of small bowel malignancy. In one study of patients with small intestinal malignancy, 12% had a history of cholecystectomy, and of those with duodenal adenocarcinoma, 25% had prior cholecystectomy. However, a causative relationship between cholecystectomy and small intestinal adenocarcinoma has not been identified.

HIGH-RISK POPULATIONS

Several heritable and inflammatory gastrointestinal conditions are associated with an increased risk for development of small bowel tumors.

Familial Adenomatous Polyposis

Patients with familial adenomatous polyposis (FAP) carry a lifetime risk approaching 100% for the development of adenomatous polyps of the duodenum, and these lesions may progress to adenocarcinoma. FAP patients
have an approximately 300-fold increased risk for development of adenocarcinoma of the duodenum over the normal population, and this is the leading cause of cancer death in patients with FAP previously treated by colectomy. These patients require regular screening esophagogastroduodenoscopy and endoscopic or surgical excision of enlarging adenomas.

**Crohn’s Disease**

Patients with active jejunoileitis of Crohn’s disease have a 100-fold increased incidence of adenocarcinoma. Active disease in the terminal ileum is the most frequent site of malignancy. Abdominal complaints and symptoms consistent with their primary condition may delay evaluation and diagnosis, leading to detection of tumors at advanced stages. The prognosis for patients with adenocarcinoma arising in Crohn’s disease is poor. For patients undergoing bowel-preserving procedures such as stricturoplasty, a biopsy of the site of past or active disease is advised to rule out dysplasia or in situ carcinoma. Such findings, while rare, would warrant resection rather than bowel-preserving approaches.

**Celiac Disease**

Celiac disease is associated with increased risk of lymphoma, which develops in up to 14% of patients. A gluten-free diet has been postulated to decrease this risk, although this has not been substantiated.

**Posttransplantation Lymphoproliferative Disorder**

Patients on chronic immunosuppression therapy are at particular risk for small bowel malignancies, especially lymphomas and sarcomas. Transplant recipients on immunosuppression have a 45- to 100-fold increase in non-Hodgkin lymphoma (NHL), a condition termed posttransplantation lymphoproliferative disorder (PTLD). The incidence of PTLD ranges from 1% to 20% of solid organ transplants and is usually of B-cell origin, with Epstein-Barr virus (EBV) being the most important risk factor. PTLD accounts for 30% of all malignancies in cyclosporine-treated patients, but
accounts for only 12% of malignancies in patients without cyclosporine in their regimen. PTLD tends to develop rapidly, with 47% of cases occurring within the first 6 months after transplantation and 62% of cases occurring within 12 months of transplantation, although risk continues for as long as immunosuppressive therapy is ongoing. Greater degrees of immunosuppression carry greater risk for development of PTLD. As transplant patients continue to live longer, it is anticipated that the incidence of PTLD will increase.\textsuperscript{11}

**Miscellaneous Conditions Associated With Small Bowel Neoplasms**

Patients with Peutz-Jeghers syndrome develop benign hamartomas throughout the intestinal tract. Surveillance is indicated, as these lesions are at risk of malignant transformation into adenocarcinoma.\textsuperscript{12} Patients with von Recklinghausen disease may develop neurofibromas in the gastrointestinal tract that can undergo malignant transformation. HIV infection is also associated with the development of lymphoma in up to 30% of patients. Most are extranodal, and the gastrointestinal tract is the involved site in 10% to 25% of cases. More than 90% of patients present with stage IV disease, and median survival is 6 months.

**CLINICAL PRESENTATION**

Patients with small bowel tumors present with nonspecific gastrointestinal and constitutional complaints. In hindsight, the gradual development of symptoms is usually evident. The most common symptoms include vague abdominal discomfort and cramps, gradual weight loss, anemia, nausea, and vomiting. These nonspecific complaints, coupled with the fact that most patients are older and often on medications that may also elicit these complaints, result in a high rate of misdiagnosis and delay in diagnosis. In most series, the average duration of symptoms prior to diagnosis ranges from weeks to many months. Initial diagnostic evaluation to exclude more common conditions that can cause such signs and symptoms, including evaluation of the gastroduodenum, colon, and biliary tract, is completed, but when negative, further evaluation of the small bowel may be delayed or
deferred.

Benign lesions rarely cause abdominal pain or obstruction; rather, their presence is often heralded by acute gastrointestinal hemorrhage. Benign neoplasms may grow to a large size prior to detection and may simply be discovered incidentally on a radiologic exam or at laparotomy.

**DIAGNOSIS**

The diagnosis of small bowel tumors is hampered by a number of factors. In addition to the fact that these are rare tumors that produce nonspecific gastrointestinal complaints, the ability to fully image and observe the small intestine is challenging. With the introduction of capsule endoscopy and wider availability of small bowel enteroscopy, which allows for luminal visualization of the entire small bowel mucosal surface, accurate preoperative diagnosis is more common prior to surgery.\(^\text{13}\)

History and physical exam are nonspecific. Abdominal mass, hemepositive stool, or signs of intestinal obstruction are usually absent. Laboratory data may demonstrate iron deficiency anemia in a minority of patients.

Plain abdominal films are an appropriate initial diagnostic test, although they are rarely helpful unless the patient presents with obstructive symptoms.

**Imaging**

After ruling out more common conditions that elicit similar gastrointestinal and abdominal complaints with endoscopic evaluation of the gastroduodenum and colon, computed tomography (CT) of the abdomen is the appropriate initial imaging test. CT may reveal bulky tumors (Fig. 39-1C) or subtler findings suggestive of small bowel tumors, such as thickening of the small bowel wall. Thickening of the bowel wall to greater than 1.5 cm or the detection of discrete mesenteric lymph nodes or masses greater than 1.5 cm in diameter is highly suggestive of malignancy. If obstructing lesions are present, CT scan may reveal a transition zone demarcating dilated proximal bowel from decompressed distal bowel.
FIGURE 39-1 Imaging of small bowel tumors. A. Magnetic resonance imaging showing intraluminal filling defect in the duodenum in a patient with occult gastrointestinal blood loss anemia. The lesion proved to be a neuroendocrine tumor (carcinoid). B. Octreotide scan of the same patient showing a focus of enhanced radioactivity corresponding to the duodenal filling defect. C. Sarcoma of the jejunum. Bulky mass with near luminal obstruction in a patient presenting with signs of small bowel obstruction. D. GIST tumor as lead point for intussusception in the jejunum. Patient presented with intermittent abdominal pain and obstruction.

Tumors of the distal small bowel may cause jejunoileal or ileocolic intussusception (Fig. 39-1D). During intussusception, the small bowel tumor serves as the lead point to pull the small bowel into the distal small bowel or colonic lumen; the mass lesion precludes spontaneous reduction. CT findings
of ileocolic or jejunoileal intussusception include the presence of concentric rings with a donut appearance involving the bowel. A luminal mass may be seen on CT or magnetic resonance (MR) contrast studies (Fig. 39-1A). This sign is nearly pathognomonic for small bowel tumor. In adults, radiographic attempts to reduce an intussusception should not be attempted. Rather, prompt surgical exploration and resection of the nonreduced intussuscepted bowel segment with mesenteric resection should be completed without intraoperative attempts at reduction.

Although a number of SI-NETs are metabolically active and express hormones, somatostatin scintigraphy (octreotide scanning) is of minor value in most cases to detect a primary SI-NET, although occasionally such a study is diagnostic (Fig. 39-1B). Positron emission tomography (PET) scanning also has limited utility in providing a discriminate diagnosis, as there is significant overlap between benign and malignant conditions. More recently, PET-DOTATATE scans have been introduced for identification and staging of these tumors, and this modality was recently approved by Medicare. Although diagnostic methods continue to improve, many patients with small bowel neoplasms still have initial presentation as a surgical emergency, and more than half of patients with malignant disease have metastatic spread at the time of operation.

Luminal contrast radiographic studies may be used if abdominal CT imaging fails to reveal evidence of a small bowel tumor, usually an upper gastrointestinal contrast series with small bowel follow-through. A small bowel follow-through study will show an abnormality in 53% to 83% of cases, although direct evidence of a tumor is detected in only 30% to 44% of cases.

Although enteroclysis (a dynamic contrast technique using a slurry of barium and methylcellulose infused into the small bowel via a nasoduodenal tube to uniformly distend the small bowel lumen) was formerly used to study the mucosal surface of the small bowel lumen, this procedure has been largely replaced by video capsule endoscopy (VCE) and CT/MR enterography.

CT and MR enterography use negative contrast agents given orally prior to the scan to enhance imaging of the bowel wall and luminal contents. Unlike enteroclysis, these procedures do not require nasoduodenal intubation. Although luminal distention is inferior to that of enteroclysis, the ease and tolerability of the procedures have made these modalities the diagnostic
studies of choice for challenging cases. The choice of CT or MR enterography is a matter of local preference as neither modality has been shown to be superior to the other in diagnostic yield.\textsuperscript{14}

**Small Bowel Endoscopy**

VCE is now widely used in the diagnosis of small bowel tumors in patients with otherwise negative diagnostic studies. The device is an ingestible 11 × 26 mm capsule, swallowed by the patient, that contains a miniature video camera, light source, battery, and transmitter that sends images (up to 50,000 overall) to a recording device worn by the patient. Currently, the device does not have the capacity for biopsies or for precise localization of lesions, although relative position can be discerned. The device can be very useful in identifying lesions within the lumen of the small bowel. The major complication of VCE is capsule retention, which is reported in 5% of cases, although the rate of requirement for surgical retrieval is less than 1%.\textsuperscript{15}

Direct luminal examination of the small bowel is best accomplished with double-balloon enteroscopy (DBE). Using an enteroscope, overtube, and balloon-pump system, a series of push-and-pull maneuvers are used to intubate more of the bowel either antegrade or retrograde. Although, procedures are longer with DBE, some studies have shown advantages in depth intubated and increased findings requiring treatment.\textsuperscript{16}

With widespread availability and utilization of VCE and DBE, the detection of small bowel tumors has increased. An advantage of DBE is the ability to obtain biopsy tissue for diagnosis and to place localizing tattoos to guide subsequent surgical resection.

Intraoperative enteroscopy, coupling surgically facilitated intubation of the small bowel with direct extraluminal observation during surgery, allows a more complete evaluation of the small bowel. It is of value in detection of occult bleeding from the small bowel but is rarely used for the diagnosis of small bowel tumors, because most can usually be readily identified by careful palpation or visualization of the bowel once operation is pursued.\textsuperscript{13,16}

**BENIGN TUMORS OF THE SMALL INTESTINE**

Although they account for 30% to 50% of primary neoplasms of the small
bowel, benign tumors are poorly characterized. Half of patients with benign tumors are symptom free, and most will be diagnosed at the time of presentation with a surgical emergency such as obstruction, gastrointestinal hemorrhage, or perforation. Gastrointestinal bleeding is the most common presenting complication, presumably a consequence of spontaneous necrosis when the benign lesion outgrows the available blood supply.\(^5\)

Once these lesions are diagnosed, surgical segmental intestinal resection is appropriate. Although local excision via endoscopic mucosal resection or operative enterotomy with submucosal excision is feasible, it is generally not possible to grossly differentiate between benign and malignant lesions. Hence, transmural resection is preferred for indeterminate lesions. Open and laparoscopic approaches have been described.

**Brunner Gland Adenomas**

Brunner gland adenomas are rare tumors of the proximal duodenum.\(^17\) Originating in the Brunner glands of the duodenal submucosa that secrete alkaline bicarbonate-rich fluid and mucus, the pathogenesis of glandular hyperplasia and subsequent adenoma formation from this cell population remains unknown. Although Brunner gland adenomas have not been described to transform into carcinomas, endoscopic mucosal resection is advised to prevent complications including acute and chronic bleeding.

**Adenomas**

As in the colon, small bowel adenomas are histologically classified as tubular, tubulovillous, or villous. Most common in the periampullary region, they can develop throughout the small bowel mucosa. Increased size correlates with malignant potential, and excision is advised when diagnosis is established, often as an incidental finding. Adenomas larger than 2 cm in diameter should be considered worrisome for malignancy. Large, periampullary duodenal adenomas may present with obstructive jaundice. In these cases, ultrasound will reveal evidence of biliary obstruction, prompting upper endoscopy with endoscopic retrograde biliary and pancreatic duct evaluation (endoscopic retrograde cholangiopancreatography), which will reveal the presence of the ampullary lesion. Without these physical signs to
direct the workup, duodenal adenomas are detected during evaluation of gastrointestinal blood loss or other abdominal complaints, with either contrast upper gastrointestinal series or esophagogastroduodenoscopy (EGD), which are equally sensitive in most series. Adenomas usually appear as intraluminal filling defects and may be pedunculated. CT scan may differentiate adenoma from carcinoma, as carcinomas are often associated with bowel wall thickening. Endoscopic ultrasound is most useful in the evaluation of duodenal adenomas to evaluate depth and to determine if mucosal excision or surgical resection is more appropriate. Transduodenal local excision for small lesions is appropriate, whereas lesions >3 cm in size have a high rate of associated malignancy and are most appropriately treated with either pancreas-sparing duodenectomy or pancreaticoduodenectomy for larger lesions or periampullary tumors in suitable operative candidates. Surgical series of resected ampullary adenoma report in situ or frank adenocarcinoma in 34% to 40% of patients. Local recurrence is common for periampullary adenomas treated with excision only; recurrence rate was 40% at 10 years, 25% of which were malignant, in a retrospective series from the Mayo Clinic. For patients treated with excision only, annual surveillance with endoscopy is appropriate.

Lipomas

Lipomas of the gastrointestinal tract are typically identified as incidental findings on abdominal imaging. They rarely cause symptoms, although as polypoid, compressible intraluminal lesions, they may serve as lead points for intussusception. Lipomas are circumscribed lesions arising in the bowel wall appearing as fat density on CT imaging. Small tumors under 2 cm require no intervention, whereas larger lesions or growing lesions should be resected to rule out malignant liposarcoma.

Hamartomas

The hamartoma is the characteristic lesion of Peutz-Jeghers syndrome, an autosomal dominant condition characterized by multiple gastrointestinal hamartomas and mucocutaneous pigmentation. The tumors are widely distributed throughout the bowel in affected individuals and, in rare cases, are
associated with intussusception, bleeding, or obstruction. While malignant transformation has been described, this is a rare event. Given the broad distribution of the tumors, prophylactic excision is not feasible and surgical intervention is appropriate only to treat complications caused by the tumors.\textsuperscript{12}

**Hemangiomas**

Hemangiomas are rare congenital lesions of the small bowel. They appear to grow slowly and may become symptomatic in midlife, when acute or chronic bleeding may develop. Arising from the submucosal vascular plexuses, hemangiomas are usually solitary and not at risk for malignant transformation. Hemangiomas associated with bleeding should be locally excised or resected with a limited small bowel resection. Endoscopic sclerotherapy or angiographic embolization has also been reported as a treatment option depending on the size and position of the tumor.

**Leiomyomas**

Leiomyomas are rare benign tumors arising from the smooth muscle and stromal cells of the small intestine. Comprised of benign-appearing smooth muscle and stromal cells, they are distinguished from GISTs by molecular features, notably the absence of \textit{cKit} mutations. These benign lesions are typically clinically silent. Often growing as extraluminal pedunculated lesions, they may present with mucosal ulceration, particularly in tumors originating in the duodenum; gastrointestinal hemorrhage; and bleeding. Symptomatic lesions warrant surgical resection (Fig. 39-2C).
FIGURE 39-2 Gross appearance of tumors of the small intestine. **A.** Primary adenocarcinoma of the ileum demonstrating circumferential, extensively ulcerated, irregular mass on the mucosal surface with transmural tumor invasion showing thickening and retraction of the bowel wall. Diagnosis was established by CT with CT enterography. **B.** Renal cell carcinoma metastatic to the jejunum. This hemorrhagic focal lesion presented with occult gastrointestinal bleeding. Diagnosis was established by video capsule endoscopy. **C.** Leiomyoma of the second portion of the duodenum. This pedunculated extraluminal lesion presented in a patient with abdominal pain. A Whipple resection was performed anticipating GIST tumor. Final pathology revealed benign leiomyoma. **D.** GIST tumor of the ileum. Patient presented with intussusception diagnosed by CT. Surgical resection of nonreduced bowel performed.
MALIGNANT NEOPLASMS

The small bowel can give rise to a number of different primary tumors and is also a site for metastasis from tumors of other origins. Primary malignancies include adenocarcinoma, GIST, carcinoid, lymphoma, and leiomyosarcoma, with rare reports of other lesions including liposarcoma, myxoliposarcoma, and lymphangiosarcoma. Metastatic tumors may come from any other cancer, but the most common metastatic lesions are from melanoma and lymphomas.

Malignant tumors are much more likely to elicit symptoms than benign tumors, including abdominal pain, weight loss, anorexia, and acute or chronic blood loss. As a group, patients with malignant small bowel tumors present at advanced stages and have a poor prognosis.

Up to 30% of patients with small bowel malignancy develop a second primary tumor in another organ. For patients with SI-NET (carcinoid) tumors, the incidence of second primaries is 50%. The second primary cancer may arise in any organ, but the most frequent second primary sites are the colorectum and breast. 20,21

Adenocarcinoma

EPIDEMIOLOGY

Adenocarcinoma accounts for about 35% of small bowel tumors, making it the most common primary malignancy. 7 The frequency of small bowel tumors decreases along the length of the small bowel, with 80% located in the duodenum and proximal jejunum. Men are slightly more likely to develop adenocarcinoma than women. Risk factors for development of adenocarcinoma include polyposis syndromes, Crohn’s disease, and celiac disease.

CLINICAL PRESENTATION

Clinical presentation is dictated by the size and position of the tumor. Large tumors form the classic circumferential annular “apple core” constriction, leading to obstruction with symptoms of anorexia, vomiting, and crampy pain. Periampullary lesions may cause biliary obstruction with secondary jaundice. Absent advanced or strategically placed lesions with obstruction,
the only complaint may be vague, persistent abdominal pain.

**DIAGNOSIS**

For patients with advanced lesions, plain abdominal films may show gastric distention or proximal small bowel obstruction. For the jaundiced patient, ultrasound or abdominal CT or MR cholangiopancreatography (MRCP) may demonstrate the duodenal mass and site of biliary obstruction. Upper gastrointestinal contrast studies and EGD have equal diagnostic rates of 85% to 90%, but EGD allows diagnostic tissue biopsy. CT reveals approximately 50% of small bowel adenocarcinomas, and the appearance is that of a heterogeneous infiltrating mass. Despite diagnostic strategies, preoperative diagnosis of cancers beyond the duodenum is achieved in only 20% to 50% of cases.

**MANAGEMENT**

Surgical resection offers the only potential cure (Fig. 39-2A). Many patients have intra-abdominal metastases at initial surgery, with R0 resection (ie, no gross or microscopic disease left) achieved in only 50% to 65% of cases. Pancreateoduodenectomy is appropriate for proximal duodenal tumors. In the third and fourth portions of the duodenum and in the mesenteric small bowel, a segmental resection with lymphadenectomy should be performed. Palliative procedures to relieve obstruction or control hemorrhage should be completed at the time of exploration for patients with metastatic disease. Endoscopic expandable stents may be the best strategy to palliate proximal gastrointestinal obstruction from recurrent or metastatic disease. Gastrojejunual bypass or gastrostomy tubes may be of palliative value for decompression or nutritional support in patients with carcinomatosis or unresectable disease.

**STAGING AND PROGNOSIS**

The American Joint Committee on Cancer staging system applies to small bowel adenocarcinoma. The tumor (T) classification describes depth of invasion, with T1 and T2 lesions within the bowel wall and T3 and T4 lesions penetrating the bowel wall. The node (N) classification is defined by the
presence or absence of lymph node metastases, and distant metastases are
classified by M. Most patients present with stage III (lymph node
involvement) or stage IV disease (distant metastases), which carry a poor
prognosis.

The most significant prognostic factor is lymph node metastases, with
poor survival linked to node-positive disease. Likely due to limited reported
experience, the primary tumor features, including the degree of
differentiation, do not appear to impact survival. Positive margins, extramural
venous spread, positive lymph nodes, and a history of Crohn’s disease are
associated with poor prognosis.6

Adjuvant therapies including chemotherapy and/or radiation therapy have
not demonstrated efficacy, although clinical trials are ongoing.20 The rare
nature of this tumor, with advanced-stage presentation, precludes
development of clinical trials.

Non-Hodgkin Lymphoma

The gastrointestinal tract is the most common extranodal site for
development of NHL, comprising approximately 20% of all cases of NHL.
Most gastrointestinal lymphomas arise in the stomach (60%), followed by the
small bowel (30%), and then the colon. Small bowel lymphomas are
distributed in the jejunum and ileum, reflecting the distribution of lymphoid
tissue in the bowel. Diagnostic criteria for primary gastrointestinal NHL
include the absence of superficial adenopathy on physical examination,
absence of mediastinal adenopathy by chest imaging, normal peripheral
blood cell counts, and absence of splenic or hepatic involvement. At surgery,
disease must be restricted to the primary tumor with mesenteric lymph node
involvement.23

The majority of cases of primary intestinal NHL are B-cell type with T-
cell lymphoma composing only 10–25%. Low-grade lymphomas derived
from mucosal-associated lymphoid tissue (MALT) typically arise in the
stomach in association with Helicobacter pylori infection. These tumors may
regress with treatment of this infection.24,25 T-cell lymphomas tend to have a
worse prognosis than B-cell tumors.

CLINICAL PRESENTATION
The majority of patients present with nonspecific abdominal complaints. Malabsorption, obstruction, or palpable mass may be present. Although rare, small intestinal lymphomas may present with perforation.

**DIAGNOSIS**

Lymphomas may grow to large size before clinical symptoms present. Most small bowel lymphomas will be demonstrable on CT scan as a mass, bowel wall thickening, displacement of adjacent organs, or luminal obstruction. Multiple lesions are present in 10% to 25% of patients. Tissue diagnosis requires biopsy of the submucosal lesion by endoscopy or CT-guided biopsy.

**STAGING AND PROGNOSIS**

Staging is based on site involvement as outlined in Table 39-1. Like tumors elsewhere in the small intestine, most patients present with stage III or IV disease. Fewer than 30% of patients have surgically resectable tumors, and prognosis is poor.\(^22\)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region; or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of 2 or more lymph node regions on the same side of the diaphragm; or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement, with or without involvement of other lymph node regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm, which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement, or by involvement of the spleen, or both</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of 1 or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s); any involvement of the liver or bone marrow, or nodular involvement of the lungs</td>
</tr>
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**TREATMENT**

With no randomized series and small series at single institutions, the optimal treatment of gastrointestinal NHL remains controversial. Most agree that surgical resection of isolated small bowel lymphoma for local control and prevention of perforation and bleeding are the cornerstones of treatment. For more extensive gastrointestinal lymphoma, there is no evidence-based consensus on optimal management, although a variety of chemotherapeutic regimens have been used.\(^{23,24}\)

**SMALL INTESTINAL NEUROENDOCRINE**
TUMORS

SI-NETs, previously known as carcinoid tumors,\textsuperscript{26} arise from the enterochromaffin cells at the base of the crypts of Lieberkühn. This redesignation was initiated based on the recognition that these tumors share cellular origin and synthetic capability of NETs originating throughout the mucosal surfaces of the body. Enterochromaffin cells are capable of amine precursor uptake and decarboxylation (APUD), and tumors derived from these can secrete vasoactive peptides responsible for the carcinoid syndrome. Eighty percent of NETs arise in the gastrointestinal tract, 10% in the bronchus or lung, and others in rare sites including the ovaries, testicles, pancreas, and kidneys. The appendix is the most common site in the gastrointestinal tract for primary NET, followed by the small bowel where these tumors are noted as SI-NETs (Table 39-1). Thirty percent of SI-NETs arise in the jejunum or ileum and have the most aggressive clinical features.

SI-NETs represent 5% to 35% of small bowel neoplasms; the mean age of presentation is 60 years with a slight male preponderance. Autopsy rates reveal that the incidence of occult tumors is approximately 2000 times that of the annual clinical incidence rate, indicating that the overwhelming majority never develop clinical findings.\textsuperscript{24,27}

CLINICAL PRESENTATION AND DIAGNOSIS

Most SI-NETs grow slowly and have insidious clinical manifestations; in hindsight, symptoms may be present for 2 to 20 years before diagnosis. Carcinoid syndrome secondary to metastatic disease is the presenting sign in 40% of patients. Rarely, intestinal necrosis secondary to desmoplastic occlusion of the mesenteric vessels may develop, leading to initial presentation as a surgical emergency.

The most common presenting symptom for patients with SI-NET is abdominal pain. The polypoid lesion serves as a lead point for intussusception characterized by intermittent symptoms and signs of obstruction. Abdominal films often demonstrate a distal small bowel obstruction, and the CT findings of intussusception are distinctive, demonstrating a multilayer ringed structure in the ileocolic region (Fig. 39-3).
FIGURE 39-3 Concentric rings in the soft tissue mass in the right lower quadrant reveal an ileocolic intussusception. An ileal carcinoid tumor was the lead point.

Appendiceal NETs are typically solitary lesions. However, for carcinoids arising in other areas of the gut, multiple tumors are observed in 3% to 40% of patients. In addition, 30% to 50% of SI-NETs are associated with second primary malignancies, most frequently of the breast and colon. SI-NETs have the capacity to elicit a marked desmoplastic reaction in the mesentery of the small bowel. The fibrotic reaction can cause sclerosis of mesenteric vessels, leading to kinking of the bowel or intestinal ischemia and necrosis. The fibrosis affects not only peritumoral tissues but also distant tissues in the heart and lungs and is attributed to the humoral products of the tumors, although the specific factors are unknown.

STAGING AND PROGNOSIS

Appendiceal NET, even at a small size, may cause appendicitis due to
luminal compression; hence, early diagnosis of appendiceal carcinoid is common. In contrast, SI-NETs exhibit a more aggressive phenotype and are frequently associated with lymph node spread and hepatic metastasis at initial presentation. Tumor size is proportional to the risk for metastatic spread. For SI-NETs smaller than 1 cm, there is a 20% to 30% incidence of nodal and hepatic spread. Tumors 1 to 2 cm in size have nodal spread in 60% to 80% of cases and hepatic disease in 20% of cases. The rates of nodal and hepatic metastasis for tumors larger than 2 cm is >80% and 40% to 50%, respectively.\(^{27}\) Only very small SI-NETs (ie, <1 cm) can be treated with local excision. All others should be treated with segmental bowel and mesenteric resection.\(^{31}\)

**CARCINOID SYNDROME**

Carcinoid syndrome refers to vasomotor, gastrointestinal, and cardiac manifestations induced by systemic circulation of peptides produced by carcinoid tumors. The APUD cells of carcinoid tumors can produce vasoactive products including serotonin, histamine, kallikrein, bradykinin, and prostaglandins, although the specific mediator or mediators of the syndrome remain unknown. Carcinoid syndrome is confirmed by finding elevated 24-hour 5-hydroxyindoleacetic acid (5-HIAA) urinary excretion, the primary stable metabolite of serotonin. In addition to 24-hour urinary 5-HIAA, disease burden may also be assessed by plasma chromogranin A levels; other biomarkers including pancreastatin have been described.\(^{32}\)

Attacks are characterized by intense flushing and tachycardia. Watery diarrhea, at times explosive and associated with cramping, may occur in some patients. Attacks may be spontaneous or precipitated by stress, alcohol, a large meal, or sexual intercourse. Flushing, a 5- to 10-minute sensation of heat associated with facial and truncal erythema, is the most common finding and affects approximately 80% of patients. Diarrhea occurs in most patients and is likely related to serotonin release, as serotonin antagonists can effectively treat this symptom. Abdominal cramps and malabsorption may occur. Cardiac manifestations are present in 60% to 70% of patients with advanced disease, due to tricuspid and pulmonary valve endocardial fibrosis, possibly secondary to high levels of 5-HIAA. As the disease progresses, the fibrotic plaque stiffens, leading eventually to right heart failure.

Carcinoid syndrome is due to metastatic tumor in either the liver or
retroperitoneum. Monoamine oxidase in the liver metabolizes serotonin to metabolites without vasomotor activity, one of the major effector hormones. Carcinoid syndrome occurs when metabolically active tumor is present in a site without portal drainage, such as a bronchial carcinoid or retroperitoneal tumor, or when hepatic metastatic tumor burden exceeds the capacity of hepatic monoamine oxidase to metabolize serotonin. Patients with gastrointestinal NETs that drain into the portal circulation must have metastatic disease prior to the development of the syndrome.

Management of patients with carcinoid syndrome due to metastatic hepatic tumor burden is optimized by utilization of surgical, image-guided interventional procedures and medical therapies. Given the relatively slow growth of NETs, including metastatic disease, surgical debulking of extensive hepatic disease or formal hepatic resection for resectable metastases can improve symptoms and prolong life. Five- and 10-year survival for patients with residual abdominal tumor and hepatic metastases exceeds 60%. While in general the initial surgery for resection of NET burden, including hepatic metastases, should attempt to debulk as much tumor as possible, the procedure must be planned to avoid catastrophic injuries, such as those to the superior mesenteric vessels, that could lead to short-gut syndrome. Hepatic artery embolization or radiofrequency ablation may be more appropriate for widespread hepatic metastases and can give marked symptomatic relief and durable tumor control.

Medical therapy is based on somatostatin analogues (octreotide), including short- and long-acting peptides for relief of carcinoid syndrome symptoms. NETs express somatostatin receptors, and the somatostatin analogues inhibit vasoactive peptide release from carcinoid tumors. Palliation of symptoms is effective in 90% of patients with octreotide. Some studies have demonstrated a tumor static or tumor reduction effect after the administration of somatostatin, although these latter findings have not been consistently reproduced. Efficacy of treatment can be documented by following excretion of tumor markers.

Chemotherapeutic agents for the treatment of metastatic carcinoid tumor include doxorubicin, fluorouracil, dacarbazine, and interferon-α, with response rates of approximately 20%. Combination protocols most often use streptozotocin and fluorouracil. Newer regimens include everolimus.

Preliminary reports on the use of targeted radiotherapeutics have been presented. Somatostatin analogues bind to somatostatin receptors on
carcinoid tumors with high affinity. After binding, the ligand-receptor complex is internalized. This internalization has led to the development of “smart bombs,” which are radiolabeled somatostatin analogues that theoretically deliver radiation specifically to carcinoid cells. Indium-labeled pentetreotide demonstrated an enhanced tumor regression response compared to unlabeled analogue in one study. However, these labeled moieties have not proven as effective as surgical resection or ablative procedures and therefore should be considered secondary options.

**Gastrointestinal Stromal Tumors**

Although GISTs are the most common nonepithelial mesenchymal tumors of the small bowel, they are rare tumors of the gastrointestinal tract, representing only 0.2% of all gastrointestinal tumors. Approximately 30% to 35% of GIST arise in the small bowel, with 50% to 60% gastric and 5% colon and rectal in origin. Men and women are equally at risk, and peak incidence occurs in patients age 50 to 70 years. Rarely, tumors can arise in patient younger than 20 years of age, usually in the setting of familial syndromes such as Carney triad, familial GIST syndrome, and neurofibromatosis type 1. GIST tumors arise from the interstitial cells of Cajal, the pacemaker cells of the GI tract intercalated between the intramural neurons and the smooth muscle cells. The molecular diagnostic feature of GIST is the presence of activating c-kit mutations, a transmembrane receptor tyrosine kinase involved in the regulation of cellular proliferation, apoptosis, and differentiation. More than 90% of GISTs express kit (CD117) mutations, a molecular marker that distinguishes them from histologically similar mesenchymal tumors of the small bowel including leiomyomas, leiomyosarcoma, schwannomas, and others. Retrospective molecular analysis of mesenchymal tumors has led to reclassification of up to 70% of small bowel tumors as GISTs that had previously been classified as a variety of mesenchymal tumors.

GISTs are characterized by indolent clinical symptoms including vague abdominal pain, weight loss, and occult gastrointestinal bleeding. Of all small bowel tumors, GISTs often grow to a large size before surgical presentation. They tend to grow insidiously as extraluminal masses from their submucosal origin in a noninvasive manner, characteristically pushing adjacent organs
away from the expanding mass. Gastrointestinal hemorrhage may develop in patients with necrotic GIST in communication with the bowel lumen.

Given the propensity of GISTs to grow to a large size prior to diagnosis, CT scan is most likely to be the initial positive test. A characteristic finding is the presence of a large space-occupying mass, often with evidence of central necrosis and compression of adjacent organs and calcifications.

Regardless of size, all GISTs should be considered to be malignant. Malignant potential is determined by 2 major criteria: tumor size and mitotic rate. Biologically aggressive tumors are large tumors with a high mitotic index, whereas tumors with benign features are small and exhibit a low mitotic index. Thus, tumors are classified ranging from very low to high risk for malignant potential, a classification that has prognostic significance (Table 40-2).

**TREATMENT**

Surgery is the primary therapeutic option, with the goal being complete resection. At operation, wide local excision of the primary tumor to achieve gross negative margins with incontinuity resection of adherent organs is appropriate to attain curative resection (Fig. 39-2D). Lymph node metastasis is rare, negating the need for wide mesenteric resection. Laparoscopic resection has been shown to be safe and oncologically sound.

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**TABLE 39-2: PROGNOSTIC FEATURES OF SMALL BOWEL GASTROINTESTINAL STROMAL TUMORS**
MOLECULAR THERAPEUTICS AND GIST

Given the central role of activating mutations in the tyrosine kinases KIT and, more recently, platelet-derived growth factor receptor alpha (PDGFRA) in the pathogenesis of GIST, this tumor has served as a prototype for molecular therapeutic drug development. Activation of KIT leads to phosphorylation of a receptor substrate protein, initiating an intracellular phosphorylation cascade leading to nuclear activation of transcription events, resulting in cell proliferation and survival. The discovery of a drug that inactivates KIT with a safe therapeutic margin has revolutionized the treatment of metastatic GIST. Imatinib mesylate is a small molecule that occupies the adenosine triphosphate binding pocket of the KIT kinase domain, blocking phosphorylation of the receptor and intracellular signaling. This binding arrests cellular proliferation and survival signaling.

Clinical use of imatinib is now routine in the management of GIST. This oral agent is well tolerated and highly effective for patients with metastatic GIST. While complete regression of tumor is rare, partial regression of disease and arrest of progression of disease can be achieved for durable intervals with continuous treatment in up to 80% of patients. Efficacy of treatment can be predicted and followed using fluorodeoxyglucose-PET scanning; these highly biologically active tumors will become metabolically silent with imatinib therapy in patients with responsive tumors. Emergence of
resistant clones within tumors has been recognized with prolonged use of imatinib. Some patients show a partial response or lack of disease progression with dose escalation of imatinib. However, newer receptor tyrosine kinase inhibitors, including sunitinib malate and regorafenib, have demonstrated efficacy for patients with tumor recurrence and resistance to imatinib with increased progression-free and overall survival.\textsuperscript{39,40}

Neoadjuvant use of imatinib has been shown to result in a 70% response rate, yet based on current available evidence, it is still unclear whether preoperative therapy for GIST results in a clinically significant effect, leading to increased resectibility or enhanced long-term survival.\textsuperscript{41} The efficacy of imatinib in the adjuvant setting has been evaluated in the American College of Surgeons Oncology Group Z9001 trial, which found improved disease-free survival for patients with tumors greater than 3 cm who received imatinib.

\section*{Metastatic Lesions to the Small Bowel}

Although metastases to the small bowel are rare as a group, they are more common than primary small bowel neoplasms.

Metastatic spread can occur by direct invasion, hematogenous spread, or intraperitoneal seeding. Colon and pancreatic cancers are the most common primary sites for direct invasion. Hematogenous metastases spread most frequently from lung and breast carcinoma or melanoma. Peritoneal seeding may arise from any intra-abdominal malignancy including gastric, hepatic, ovarian, appendiceal, and colonic primary tumors.\textsuperscript{42}

CT scan may identify metastatic lesions or reveal sites of partial or complete luminal obstruction. Metastases can be identified as bowel wall thickening or mesenteric masses. For small lesions, CT scan may be negative, whereas small bowel follow-through studies may reveal an irregular luminal filling defect. Carcinomatosis is frequently not specifically identifiable on imaging studies, although PET-CT is useful for identification of small bowel metastases in some tumor types.

Optimal palliative management is based on clinical criteria. Segmental intestinal resection (Fig. 39-2B) or bypass to relieve hemorrhage, obstruction, or pain is indicated except in late terminal stages of disease. Although cases of prolonged survival after intestinal resection of solitary metastases have been reported, progression of metastatic disease is more common.
Management of patients with carcinomatosis, regardless of tumor origin, remains challenging. Endoscopic luminal stents for obstructing duodenal lesions may offer short-term palliation, whereas intestinal bypasses and decompressive gastrostomy tubes are indicated for patients with advanced or more distal disease to enhance palliative care.

REFERENCES


INTRODUCTION

The term “karzinoide” was first used in 1907 by pathologist Siegfried Oberndorfer to describe small intestinal tumors that resembled carcinomas on histology, but behaved less aggressively clinically. In the current literature, carcinoids refer to well-differentiated, low-to-intermediate-grade neuroendocrine tumors (NETs) of the bronchopulmonary and gastrointestinal (GI) tracts. By definition, NETs are epithelial neoplasms with both neural and endocrine differentiation, which arise from many different cell types of the neuroendocrine system. Carcinoids represent a diverse subset of NETs, which exhibit slow growth but variable clinical presentation, growth pattern, and prognosis, depending on anatomic site and cell of origin. This chapter describes the clinical behavior of GI carcinoids, as well as their diagnosis and management by anatomic site. It concludes with a brief description of metastatic carcinoid and carcinoid syndrome, a rare but potentially life-threatening presentation.
EPIDEMIOLOGY

GI carcinoids account for 0.5% of all newly diagnosed cancers and 71% of all NETs.\textsuperscript{5} Several large population studies have been conducted to document the incidence of GI carcinoids, their distribution across anatomic sites, and trends in incidence and outcomes over time, based on data from the national U.S. Surveillance, Epidemiology, and End Results (SEER) registry.\textsuperscript{5–7} In one series of 11,427 patients with NETs reported to SEER between 1973 and 1997, the average age at diagnosis was 61 years, and cases were distributed evenly across gender.\textsuperscript{6} The majority of NETs arose in the GI tract (55%), followed by the bronchopulmonary tract (30%), pancreas (2%), and other rare sites including, in decreasing order, gynecologic, biliary, head and neck, and genitourinary systems.\textsuperscript{6} Among GI carcinoids, the small intestine was the most common site (45%, predominantly ileum), followed by rectum (20%), appendix (17%), colon (11%), then stomach (7%) (Fig. 40-1).\textsuperscript{6} Notably, pancreatic NETs were considered separately from GI carcinoids in this study. A more recent SEER-based series of 25,531 patients with histologically confirmed GI carcinoid tumors demonstrated similar findings, with 38% of cases arising in the small intestine, 34% in the rectum, 16% in the colon, and 11% in the stomach.\textsuperscript{5} Appendiceal tumors were not considered separately in this latter analysis.
FIGURE 40-1 Small intestine is the most common site of GI carcinoid. Based on 6145 cases of GI carcinoid reported to the U.S. SEER registry. (Data from Maggard MA, O’Connell JB, Ko CY: Updated population-based review of carcinoid tumors, Ann Surg 2004 Jul;240(1):117-122.)

The incidence of NETs has increased over the past 4 decades, with one study showing an increase of approximately 0.85 to 3.84 per 100,000 between 1973 and 1997. A more recent series estimates the annual incidence of GI carcinoid tumors to be 5 per 100,000, with the largest increases noted in localized tumors and those of the small intestine, rectum, and stomach. More widespread use of axial imaging and endoscopy may partially explain this increase in diagnosis and incidence.

CLINICAL PRESENTATION

GI carcinoids generally present in one of three ways: (1) incidentally on endoscopy or axial imaging, as with many gastric and rectal tumors, or within a surgical specimen, as with an appendiceal carcinoid following appendectomy for appendicitis; (2) with locoregional symptoms, such as abdominal pain, bowel obstruction, bleeding, or bowel ischemia, due to local
tumor growth or regional nodal invasion with surrounding mesenteric fibrotic reaction; or (3) with carcinoid syndrome, ie, chronic flushing, diarrhea, and, if advanced, heart failure, most often in the setting of midgut carcinoid metastatic to the liver. The locoregional symptoms vary by primary tumor location. Intestinal obstruction and bleeding are most common with small intestinal carcinoids, rectal bleeding and pain tend to occur with rectal carcinoids, weight loss and abdominal pain are more frequently seen with colonic carcinoids, vomiting occurs with gastric carcinoids, and jaundice and upper GI bleeding are most often associated with duodenal and periampullary carcinoids.

About half of all cases present with localized disease, while another quarter each present with regional or distant metastases. Notably, patients with carcinoid tumors also have a higher incidence of additional primary cancers compared with the general population. Approximately 25% of patients harbor second malignancies of the small intestine, stomach, or extra-intestinal sites such as the thyroid and kidney.

**GENERAL TUMOR LOCALIZATION AND STAGING**

Nonspecific symptoms often necessitate further laboratory and radiologic evaluation to localize the tumor and confirm the diagnosis of carcinoid. Two commonly used biochemical tests are serum chromogranin A (CgA) level and 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA).

CgA is a glycoprotein involved in intracellular vesicular transport. It is synthesized and secreted along with other peptide hormones by many types of non-neoplastic and neoplastic neuroendocrine cells. The serum CgA level is elevated in about 90% of GI carcinoids, both functional and nonfunctional, and correlates with tumor burden. It can be falsely elevated in many settings, however, including proton pump inhibitor therapy, pancreatic and small cell lung cancer, chronic renal insufficiency, and atrophic gastritis. Therefore, it is a sensitive but nonspecific marker of GI carcinoid. As a consequence, it is less useful for screening or initial diagnosis and more suited for assessing treatment response or disease progression. Of note, CgA staining on immunohistochemical analysis is an important marker.
used in the histologic diagnosis of NETs.\textsuperscript{11}

Urinary 5-HIAA is a less sensitive but more specific test for carcinoid. A degradation product of serotonin (5-hydroxytryptamine [5-HT]), 5-HIAA is one of the most commonly secreted hormones from GI carcinoid tumors.\textsuperscript{11} At the molecular level, tryptophan is taken up by neuroendocrine cells, hydroxylated to 5-HT, decarboxylated to serotonin, then stored in granules and ultimately secreted into the bloodstream, after which it is metabolized to 5-HIAA and excreted in the urine.\textsuperscript{8} As a diagnostic test, 24-hour urinary excretion of 5-HIAA is most accurate for detecting midgut carcinoids metastatic to the liver and/or associated with carcinoid syndrome, with an estimated 70% sensitivity and 90% specificity.\textsuperscript{11} Sensitivity is lower in the absence of carcinoid syndrome, in the setting of low-volume tumor burden, or for foregut and hindgut carcinoids, which rarely produce serotonin.\textsuperscript{3,11} Specificity is limited by false positive elevations of urinary 5-HIAA, eg, in the setting of a tryptophan-rich diet.\textsuperscript{8,9} Overall, the laboratory evaluation plays a limited role in the initial diagnosis of GI carcinoid, warranting further investigation.

Endoscopy and axial imaging are essential to tumor localization and staging. Endoscopy permits tissue sampling and gross visualization of primary carcinoids arising in the stomach, duodenum, terminal ileum, colon, and rectum. Multidetector computed tomography (CT) of the abdomen and pelvis, with arterial and venous phase intravenous (IV) contrast enhancement, can sometimes detect primary GI carcinoid tumors, which appear as solid hyperattenuating intraluminal masses on multidetector CT.\textsuperscript{10}

CT is much more useful in delineating regional and distant metastases. For midgut carcinoids metastatic to regional lymph nodes, CT clearly depicts the characteristic mesenteric desmoplastic reaction, which manifests as an irregular, spiculated soft tissue mass infiltrating the mesenteric fat, often with associated calcifications, tethering, or kinking of adjacent bowel loops, and in some cases encasement of branches of the superior mesenteric vessels.\textsuperscript{10} CT is also able to detect hypervascular liver metastases with approximately 80% sensitivity and 90% specificity.\textsuperscript{9}

Magnetic resonance imaging (MRI) is useful for equivocal liver lesions. Carcinoid metastases generally demonstrate a T2-intense signal and rapid arterial enhancement with washout of contrast on later venous phase images.\textsuperscript{10} In the setting of metastatic disease or carcinoid syndrome with an
occult primary, additional nuclear imaging with somatostatin receptor scintigraphy (eg, Octreoscan) may add useful information. Somatostatin receptor scintigraphy utilizes tumor cell−specific somatostatin receptor expression and a radiolabeled somatostatin analog (eg, 111-indium pentetreotide) to localize tumor, with variable sensitivity, which is reported to be about 2% to 23% and 80% to 90% for primary and metastatic carcinoids, respectively.4,12

Tissue diagnosis is ultimately confirmed following biopsy or surgical resection. The characteristic histologic findings include the organization of neoplastic cells into nesting, trabecular, or gyriform patterns, the presence of intracellular secretory granules, and positive immunostaining for neuroendocrine markers, such as CgA, synaptophysin, and neuron-specific enolase.2,4,13 Additionally, NETs are classified according to two cellular features: (1) degree of cellular differentiation, ie, similarity to their non-neoplastic neuroendocrine cell counterparts and (2) grade, ie, proliferative rate, as measured by the number of mitotic figures per 10 high-power microscopic fields, or immunostaining with the cellular proliferation marker Ki-67.2 As previously mentioned, carcinoids are defined as well-differentiated, low-to-intermediate-grade NETs, which harbor lower malignant potential compared with poorly differentiated, high-grade neuroendocrine carcinoma (NEC).2

Several staging systems have been proposed by the American Joint Committee on Cancer (AJCC), World Health Organization (WHO), and European Neuroendocrine Tumor Society (ENETS). Although these systems vary slightly in tumor classification, they generally conform to the tumor-node-metastasis (TNM) paradigm that distinguishes localized disease from regional nodal or distant metastasis.2 Details and implications for management and prognosis are discussed by anatomic site below. Treatment guidelines are also summarized in Table 40-1. Ultimately, for any carcinoid tumor, the goal is to determine the site and extent of disease, to resect all tumor (R0 resection) if possible, and to palliate symptoms related to locoregional tumor growth and carcinoid syndrome.
### Management and Prognosis by Anatomic Site

#### Gastric Carcinoid

Gastric carcinoids, of which there are three different types, generally arise from a subset of neuroendocrine cells called enterochromaffin-like (ECL) cells, which arise in the gastric fundus and body. Under normal conditions, these cells secrete histamine and stimulate neighboring parietal cells to produce acid in response to gastrin. Consequently, gastric carcinoids usually are not associated with serotonin secretion or carcinoid syndrome.

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Size (and Related Tumor Criteria)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Type I or II &lt;1-2 cm</td>
<td>Endoscopic resection (consider antrectomy for numerous progressing Type I tumors; first treat hypergastrinemia source for Type II tumors)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm (or muscularis propria invasion, poor differentiation, positive endoscopic resection margin, suspected nodal metastasis)</td>
<td>Partial or total gastrectomy and lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td>Type III Any size</td>
<td>Partial or total gastrectomy and lymphadenectomy (with preoperative staging evaluation for metastases)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt;1 cm</td>
<td>Endoscopic resection</td>
</tr>
<tr>
<td></td>
<td>&gt;1 cm (or suspected nodal metastasis)</td>
<td>Transduodenal excision, segmental resection, or pancreaticoduodenectomy</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Any size, resectable (based on mesenteric vascular involvement)</td>
<td>Small bowel resection and high mesenteric lymphadenectomy (with preoperative staging evaluation for metastases, and intraoperative evaluation for synchronous tumors)</td>
</tr>
<tr>
<td>Appendix</td>
<td>&lt;1 cm</td>
<td>Appendectomy</td>
</tr>
<tr>
<td></td>
<td>1-2 cm</td>
<td>Appendectomy (versus right hemicolectomy)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm (or mesoappendix/base invasion, positive margin, high grade, goblet cell histology)</td>
<td>Right hemicolectomy and mesenteric lymphadenectomy</td>
</tr>
<tr>
<td>Colon</td>
<td>&lt;2 cm</td>
<td>Endoscopic resection</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm</td>
<td>Segmental colectomy and high mesenteric lymphadenectomy with total mesocolic excision (with preoperative staging evaluation for metastases)</td>
</tr>
<tr>
<td>Rectum</td>
<td>&lt;1 cm (or incomplete endoscopic resection)</td>
<td>Endoscopic resection</td>
</tr>
<tr>
<td></td>
<td>1-2 cm (or muscularis propria invasion, high grade, incomplete local excision, suspected nodal metastasis)</td>
<td>Local transanal excision (consider advanced technique, eg, TEM, for proximal or small, high-risk lesions)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm (or muscularis propria invasion, high grade, incomplete local excision, suspected nodal metastasis)</td>
<td>Low anterior or abdominoperineal resection and total mesorectal excision (with preoperative EUS or MRI to stage tumor and regional nodes, and CT to evaluate for metastases)</td>
</tr>
<tr>
<td>Metastatic Disease</td>
<td>Carcinoid syndrome</td>
<td>Somatostatin analog therapy (octreotide), for symptom control; consider palliative resection</td>
</tr>
<tr>
<td></td>
<td>Midgut carcinoid with metastases</td>
<td>Octreotide long-acting release, consider surgical resection for prolonged disease control</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; TEM, transanal endoscopic microsurgery.
syndrome. From a pathophysiologic standpoint, chronic gastrin stimulation leads to ECL cell hyperplasia and subsequent neoplasia. Importantly, the clinical behavior and management vary significantly among the three types of gastric carcinoids, as detailed below.

Type 1 gastric carcinoids are the most common form, comprising 70% to 80% of cases. These tumors arise from ECL cells in the setting of chronic atrophic gastritis, achlorhydria, and secondary gastric endocrine (G-cell) hyperplasia with hypergastrinemia. They often occur in middle-aged women and generally present as multiple nonfunctional, small subcentimeter multicentric polyps in the gastric fundus and body. Workup, as for all gastric carcinoids, includes upper endoscopy, gastric pH, and serum gastrin measurements. Laboratory evaluation also may reveal low hematocrit, iron, and vitamin B₁₂ levels in the setting of associated pernicious anemia. Most type 1 gastric carcinoids are confined to the submucosa and metastasize in fewer than 10% of cases. Given the indolent behavior of this subclass, endoscopic resection via snare polypectomy or endoscopic mucosal resection (EMR) is recommended for all type 1 gastric carcinoids smaller than 1 to 2 cm. Surgical resection is reserved for the rare lesion that is greater than 2 cm, or lesions associated with other high-risk features, such as invasion into the muscularis propria as determined by endoscopic ultrasound, poorly differentiated histology, positive endoscopic resection margin, or nodal or distant metastases. Notably, type 1 tumors tend to recur at a median duration of 24 months following resection, with a 3% risk of progression to NEC. The most recent ENETS guidelines published in 2016 recommend serial endoscopic surveillance every 24 months for newly presenting tumors, and every 12 months for recurrent disease. Interestingly, for multiple progressive type 1 tumors, antrectomy to reduce gastrin production represents an alternative but somewhat controversial management option.

Type 2 gastric carcinoids, the rarest form, comprise only 5% to 10% of cases, and similarly derive from ECL cells in the setting of hypergastrinemia. Unlike type 1 tumors, however, type 2 gastric carcinoids are associated with primary hypergastrinemia, ie, Zollinger–Ellison syndrome, which is caused by a gastrinoma that is nearly always associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome. Type 2 gastric tumors also tend to present as multiple small polyps 1 to 2 cm
in diameter that are distributed throughout the gastric fundus.\textsuperscript{4,13,16} Approximately 10% to 30% of patients develop nodal or liver metastases.\textsuperscript{4,13,16} Management is targeted toward localizing and removing the source of the hypergastrinemia first, either surgically or medically, followed by surgical resection of the localized type 2 gastric carcinoids.\textsuperscript{13,16}

Type 3 gastric carcinoids comprise 15% to 25% of cases and display pronounced aggressive clinical behavior. This form generally presents sporadically as a large solitary mass greater than 2 cm in diameter. The masses are associated with a higher incidence of local invasion through the gastric wall, higher proliferative rate on histology, and higher rate of associated nodal or distant metastases in 50% to 100% of cases.\textsuperscript{4,13,16} Patients are more often male and may present with atypical carcinoid symptoms, such as pruritus and flushing due to histamine production.\textsuperscript{16} The workup should include endoscopic ultrasound to assess the depth of tumor invasion, abdominopelvic CT, and sometimes somatostatin receptor scintigraphy to evaluate for metastatic disease. Management with radical gastrectomy and lymphadenectomy parallels the treatment of gastric adenocarcinoma.\textsuperscript{13,16}

Prognosis varies dramatically across the three gastric carcinoid types: 5-year survival is estimated to be 95% for type 1 patients, 60% to 75% for type 2, and only 25% to 50% for type 3 patients.\textsuperscript{4} Outcome also depends on extent of disease, with reduced 5-year survival rates of 73%, 65%, and 25% for local, regional, and distant disease, respectively.\textsuperscript{7}

**Duodenal Carcinoid**

Duodenal carcinoids are rare. They comprise only 2% to 3% of GI carcinoids.\textsuperscript{16,17} Unlike other small intestinal carcinoids that arise from the serotonin-producing enterochromaffin cells, sometimes in association with carcinoid syndrome, the duodenal carcinoids generally derive from either gastrin-producing G cells (gastrinoma, 50%-60% of cases) or somatostatin-producing D cells (somatostatinoma, 20%-40% of cases), and the majority of these tumors are not associated with any functional clinical syndrome.\textsuperscript{16,17} The duodenal carcinoids instead present with local symptoms such as abdominal pain, GI bleeding, or jaundice.\textsuperscript{17} The majority of these tumors originate in the proximal duodenum, ie, the first or second portions or periampullary region.\textsuperscript{17} Duodenal gastrinomas arise either sporadically or in
the context of MEN-1, in which case multiple tumors are common. Somatostatinomas are often associated with the hereditary syndrome neurofibromatosis type 1 (von Recklinghausen disease) and more frequently involve the ampulla. On presentation, duodenal carcinoids are generally small, less than 2 cm in diameter, with distant metastases in fewer than 10% of cases, but with nodal involvement in up to 40% to 60% of cases. The recommended treatment for small (≤1 cm) duodenal carcinoids is endoscopic resection. For tumors located in the periampullary region that are larger than 1 to 2 cm, or associated with nodal metastases, surgical resection with either local resection and lymphadenectomy or radical resection via pancreaticoduodenectomy should be performed, although the extent of surgical resection remains controversial. Prognosis varies by disease extent, with 5-year survival decreasing from 68% for localized disease to 55% and 46% for regional and distant metastases, respectively.

**Small Intestinal Carcinoid**

The small intestine is the most common site for GI carcinoids. Carcinoids are in fact one of the most common histologic subtypes of small intestinal neoplasms, comprising about 37% of cases, comparable to adenocarcinoma. Small intestinal carcinoids most often arise in the ileum (45%-50%), followed by the duodenum (18%), and rarely the jejunum (6%). As noted earlier, midgut carcinoids arise from a different cell type and behave differently from their foregut counterparts. Jejunoileal carcinoids derive from serotonin-secreting enterochromaffin cells and are most often associated with carcinoid syndrome, ie, flushing, diarrhea, and carcinoid heart disease. Primary small intestinal carcinoids are notoriously slow-growing, manifest with nonspecific symptoms such as cramping and bloating, and are often diagnosed late in the disease process, with nodal and distant metastases in 40% and 30% of patients, respectively. Additionally, 20% to 40% of small intestinal carcinoids are multicentric. Primary tumors are difficult to localize either radiographically or endoscopically. CT often depicts nodal involvement, with the characteristic desmoplastic mesenteric reaction (Fig. 40-2A) or distant liver metastases. Primary tumor localization therefore requires additional imaging with somatostatin receptor scintigraphy, which is reported to have increased sensitivity for small intestinal tumors.
compared with other anatomic sites, and potentially other less-studied modalities such as video capsule endoscopy and double-balloon enteroscopy.\textsuperscript{20}
FIGURE 40-2 Small intestinal carcinoid characteristically spreads to the mesentery and is associated with a desmoplastic response, seen on CT as a spiculated mesenteric mass (arrow) tethering adjacent bowel loops (A). The recommended treatment for localized small intestinal carcinoid is radical small bowel resection with high mesenteric lymphadenectomy (B), sometimes requiring skeletonization of the mesenteric vessels to remove nodal disease (C). (Used with permission from Yi-Zarn Wang, MD, Baylor University Medical Center, Dallas, TX and Eugene Woltering, MD, Louisiana State University Health Sciences Center, New Orleans, LA.)

Surgical resection is the only potential cure for small intestinal carcinoid. Resectability should be determined in the multidisciplinary setting with multimodal evaluation as above. All patients with resectable disease, ie, without prohibitive mesenteric root fibrosis, superior mesenteric artery involvement, or diffuse metastases, should undergo oncologic small intestinal resection with regional lymphadenectomy. Surgical exploration should include thorough evaluation of the entirety of the small bowel for multicentric tumors, adequate high mesenteric lymph node resection, and care to preserve as much mesenteric vasculature and bowel length as possible (Fig. 40-2B, C). Prophylactic cholecystectomy has previously been recommended owing to the increased incidence of cholelithiasis in patients treated with somatostatin analogs, but prospective studies supporting this practice are lacking, and the decision is therefore deferred to the individual clinical setting and surgeon. In patients with preoperatively diagnosed carcinoid syndrome, perioperative treatment with octreotide, a somatostatin analog, is essential to preventing carcinoid crisis, a potentially life-threatening constellation of signs including hemodynamic instability, flushing, bronchospasm, and, when severe, vasomotor collapse. In nonresectable patients, palliative resection in the setting of impending or symptomatic bowel obstruction should also be considered in the appropriate clinical context.

Prognosis varies with disease extent, with 5-year survival rates estimated to be 65%, 71%, and 54% for local, regional, and distant disease, respectively. Radical small bowel resection with lymphadenectomy was associated with improved overall survival in a retrospective review of 603 patients with small intestinal carcinoid or carcinoid syndrome in a single-institution study. Additional independent predictors of worse survival,
based on several SEER-based studies, include male gender, age greater than 55 years, African American race, tumor size greater than 1.0 cm, and involved margins.\textsuperscript{19,23} Unfortunately, no effective adjuvant therapies are currently available.\textsuperscript{21} Relatively indolent tumor growth warrants less frequent but long duration of surveillance, with an initial evaluation at 3 to 6 months postoperatively, followed by serial evaluation with history, physical exam, laboratory serum CgA and urinary 5-HIAA studies, and axial imaging with multiphasic CT or MRI at 6- to 12-month intervals.\textsuperscript{20,21}

**Appendiceal Carcinoid**

The appendix was previously thought to be the most common site of GI carcinoid but is now estimated to comprise only about 16\% of cases,\textsuperscript{6} with decreasing incidence over the past four decades.\textsuperscript{5,6} Nevertheless, carcinoid represents the most common type of appendiceal neoplasm and is discovered, often incidentally, in about 0.5\% of all appendectomy specimens.\textsuperscript{20,24} Average age at diagnosis is 40 to 50 years, younger than other sites of carcinoid, and tumors are usually small, less than 1 cm in diameter, and localized to the tip of the appendix (Fig. 40-3).\textsuperscript{7,20} Appearance on CT ranges from occult to findings suggestive of acute appendicitis, ie, diffuse thickening and adjacent fat stranding.\textsuperscript{4}
FIGURE 40-3 The majority of appendiceal carcinoids present as incidental findings on surgical pathology following appendectomy and often are small and localized to the tip of the appendix.

Tumor size correlates with malignant potential. In one SEER-based study of 89 patients with appendiceal carcinoid, nodal metastases were rare in patients with tumors 1 cm or smaller (15%), but increasingly more frequent with intermediate size tumors greater than 1 cm and less than 2 cm (47%) and large tumors greater than 2 cm (86%). Appendectomy is therefore considered adequate treatment for most appendiceal carcinoids less than or equal to 1 cm. There is little evidence to support oncologic right hemicolectomy for larger tumors, but generally accepted indications in the literature include tumor size greater than 2 cm, invasion into the mesoappendix or base of the appendix, positive margin, high grade histology, or the more aggressive goblet cell histology, ie, mixed adeno-neuroendocrine carcinoma. For intermediate-sized tumors 1 to 2 cm, some groups recommend axial imaging to evaluate for nodal or distant metastases or right hemicolectomy, but data demonstrating impact on survival are lacking.

Overall prognosis for appendiceal carcinoid is excellent, with 5-year survival just under 100%. As for other sites of GI carcinoid, survival varies with disease stage, with 5-year survival rates estimated to be 88% and 78% for localized and regional disease, respectively, but only 25% for the rare patient with distant metastases.

Colonic Carcinoid

Colonic carcinoids comprise about 11% of all GI carcinoid tumors, with 62% arising in the sigmoid or rectosigmoid junction, 21% in the ascending, 9% in the transverse, and 9% in the descending colon. While proximal colonic tumors resemble small intestinal carcinoids in regard to cell of origin (enterochromaffin cells) and serotonin production, distal colonic tumors of the hindgut more often produce glucagon-like peptide and pancreas polypeptide (PP/PYY) and are generally not associated with carcinoid syndrome. The clinical behavior of colonic carcinoids resembles that of small intestinal tumors in that patients most often present late, with over 50% harboring nodal or distant metastases at the time of diagnosis. Initial workup
should therefore include staging evaluation with IV contrast-enhanced CT of the chest, abdomen, and pelvis, plus additional metastatic evaluation with liver MRI and/or somatostatin receptor scintigraphy in the setting of clinical suspicion or equivocal CT. Tumors smaller than 2 cm may be excised endoscopically. However, most carcinoid tumors of the colon are larger than 2 cm, and in the absence of diffuse disease, require oncologic resection with segmental colectomy and mesenteric lymphadenectomy according to the principles of total mesocolic excision, similar to management of colonic adenocarcinoma. This includes full mobilization of the colon along fascial planes to expose the unfragmented mesentery at its take-off from the superior mesenteric artery (SMA). On the right, a Kocher maneuver may be necessary to achieve a high central vascular ligation of the mesentery. An extended right hemicolectomy with high ligation of the entire middle colic artery may be needed when the tumor is close to the take-off of the right branch of the middle colic artery. On the left, flush ligation of the internal mesenteric artery (IMA) on the aorta as well as high ligation of the internal mesenteric vein (IMV) may be needed, although this maneuver should not be performed unless there is a high index of suspicion for metastatic lymph nodes, as this can lead to sexual dysfunction and urological disorders.

Colonic carcinoids carry a worse prognosis than other anatomic sites, due in part to their late presentation and more aggressive biology. Five-year survival rates are worse (85%, 46%, and 14% for localized, regional, and distant disease, respectively) compared with the small intestine carcinoids. Thus, careful surgical technique at the index operation is critically important. Although laparoscopic case reports describing high-quality total mesocolic excisions with high central vascular ligation have been touted, we encourage early conversion to open surgery if and when the colonic mesentery is foreshortened and/or heavily involved with metastatic nodules.

**Rectal Carcinoid**

Carcinoids that arise in the rectum account for 20% of all GI carcinoids, rendering the rectum the second most common site of disease behind small intestine. Similar to distal colonic tumors, rectal carcinoids are rarely associated with serotonin production or carcinoid syndrome. They often are discovered incidentally on lower endoscopy. The prevalence of these tumors
has increased over the past 4 decades, and they nearly always present as small tumors localized to the submucosa (Fig. 40-4A, B).  

**FIGURE 40-4** Most rectal carcinoids are diagnosed incidentally by the appearance of a small submucosal mass on lower endoscopy (A). Endorectal ultrasound confirms submucosal tumor localization (B). (C) Local transanal excision is indicated for intermediate-sized lesions 1 to 2 cm, as well as small lesions (<1 cm) that have incomplete endoscopic excision or high-risk pathologic features. Such lesions can be excised using advanced transanal surgical techniques, such as transanal endoscopic microsurgery (TEM), transendoscopic operation (TEO), or transanal minimally invasive surgery (TAMIS). Transanal excision proceeds with cauterization of a margin 1 cm around the lesion or residual scar (i-ii), full thickness dissection to the mesorectal fat (iii), removal of the specimen en bloc without fragmentation.
Given their low risk (<3%-5%) of metastasis, rectal carcinoids smaller than 1 cm can be excised endoscopically via polypectomy or with an advanced endoscopic technique such as EMR. This statement is made with some reservation, however, since the adequacy and appropriateness of endoscopic resection depends on the following criteria: the tumor must be removed en bloc and without fragmentation, and the disease must not invade the muscularis propria or have high mitotic activity. Thirty percent of tumors resected endoscopically with close margins will have residual disease on a follow-up of local excision, highlighting the importance of transanal scar reexcision and full-thickness resection of the surrounding rectal wall with a 1-cm margin.

Local excision can also be offered to patients presenting with intermediate-size tumors measuring 1 to 2 cm in maximal diameter. Such excisions can be performed using standard transanal instruments when tumors are distal and easy to reach, or advanced transanal endoscopic microsurgery (TEM) for lesions located more proximally in the rectum. Given the current technical advances in transanal minimally invasive surgery, including TEM, transanal endoscopic operation (TEO), and transanal minimally invasive surgery (TAMIS), radical resection with total mesorectal excision for intermediate-size rectal carcinoids is rarely justified.

For the uncommon large (>2 cm) rectal carcinoid, or for tumors with high-risk features such as muscularis propria invasion, high grade classification, or incomplete resection on local excision, further evaluation should proceed with pelvic MRI or endorectal ultrasound to better assess tumor size, depth, and nodal involvement. In addition, staging CT of the chest, abdomen, and pelvis can be performed to better evaluate for distant metastases, most notably to liver. In the absence of unresectable metastatic disease, these rectal tumors should be managed with either a low anterior or abdominoperineal resection with concurrent total mesorectal excision. Tumors in the proximal rectum can be treated with a tumor-specific total mesorectal excision, provided the surgeon is able to achieve a generous distal margin of at least 5 cm of intact mesorectum measured externally, not endoscopically, below the tumor edge.

Overall prognosis is favorable for the majority of rectal carcinoid patients,
with 5-year survival rates estimated to be 90%, 62%, and 24% for localized, regional, and distant disease, respectively.\footnote{7}

**Metastatic Carcinoid and Carcinoid Syndrome**

Carcinoid syndrome most often occurs in patients who have small intestinal carcinoid metastatic to the liver. The syndrome consists of a constellation of vasomotor, GI, and cardiac symptoms thought to be mediated by peptides secreted by tumor cells into the systemic circulation, eg, serotonin, histamine, kallikrein, bradykinin, and prostaglandins.\footnote{21} The symptoms include flushing, diarrhea, wheezing in the setting of acute carcinoid crisis, and progressive right heart failure due to right-sided valvular fibrosis in severe cases.\footnote{21} Although the precise pathophysiology remains to be elucidated, carcinoid symptoms are generally attributed to elevated levels of tumor-derived hormones in the systemic circulation, ie, in the setting of large-volume metastatic burden in the liver or retroperitoneal metastasis.\footnote{21} Diagnosis is dependent on clinical findings. Supportive laboratory evaluation includes elevated 24-hour urinary 5-HIAA secretion as discussed above. Imaging studies to detect and follow metastatic disease include IV contrast-enhanced CT or MRI, and in certain settings, somatostatin receptor scintigraphy.\footnote{33}

The management options for metastatic carcinoid remain limited. Somatostatin analog therapy and surgical debulking can alleviate symptoms\footnote{21,34} and potentially aid with disease control, although data supporting the latter statement are primarily based on retrospective case series. Prospective randomized studies evaluating the effect of surgical metastasectomy on survival are lacking. Nevertheless, several large case series of patients with resected or ablated liver metastases from GI NET primaries, predominantly small intestinal carcinoids, demonstrate improved survival compared with historical controls, with 5-year survival rates up to 74%, and median survival up to 10 years, compared with 30% to 40% 5-year survival and 2- to 4-year median survival historically reported for patients with untreated hepatic metastases.\footnote{35,36} In this series, however, the 5-year recurrence rate was greater than 80% to 90%, reiterating the current goal of surgical metastasectomy, which is disease control rather than cure.\footnote{35,36}

The role of systemic therapy has been clarified in the PROMID trial, a published randomized controlled study of 85 patients with metastatic, well-
differentiated midgut carcinoid, randomized to either placebo or octreotide long-acting release (LAR). This trial demonstrated prolonged time to tumor progression (6 vs 14 months, respectively) with systemic therapy, with the greatest effect noted in patients with low tumor burden in the liver and resected primary tumor.³⁷ No difference in overall survival was detected, but the results warrant additional investigation with higher patient numbers. No other effective medical therapies exist for metastatic carcinoid. The response rate to traditional cytotoxic chemotherapy, eg, 5-fluorouracil and streptozocin, is 20% to 30% at best.²⁸ Novel agents under investigation include targeted inhibitors of the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signaling pathways,²¹ and radiolabeled somatostatin analogs for targeted radiotherapy,²⁸,³⁰ but the clinical efficacy of these newer agents remains to be proved.

GENERAL OUTCOMES

The overall prognosis for patients with GI carcinoid is excellent, with 5-, 10-, and 20-year disease-specific survival rates of 91%, 86%, and 77%, respectively.⁵ However, tumor size greater than 1 to 2 cm correlates with nodal spread, and overall survival varies significantly by disease stage (ie, nodal or distant metastases) and site of origin.⁶ Survival is notably worse with more widespread disease. Five-year disease-specific survival rates decline from 98% to 89% to 59%, respectively, for localized, regional, and distant disease.⁵ According to several large SEER-based studies, additional independent predictors of survival include site other than the small intestine, well-differentiated histology, female gender, Caucasian versus African American race, younger age, diagnosis in the most recent decade, and small primary tumor size.⁵,⁷

CONCLUSIONS

GI carcinoid tumors generally behave in a more indolent fashion compared with adenocarcinoma counterparts. Nevertheless, they represent a diverse spectrum of disease with varying malignant potential. For primary, localized disease, surgery remains the only potential cure. The goals of evaluation and management should be to localize and determine extent of disease, resect all
disease if feasible, and palliate symptoms related to locoregional tumor growth or systemic hormone-related symptoms, ie, carcinoid syndrome, with surgical resection or medical therapy—namely, somatostatin analog treatment. Medical therapies for unresectable, metastatic carcinoid remain limited and warrant further investigation.

REFERENCES


HISTORY

Although appendicitis is now well recognized as a leading cause of surgically treated abdominal pain, Galen and other early anatomists overlooked the vermiform appendix for centuries. The Renaissance artist, Leonardo da Vinci, became the first to document the existence of the appendix in sketches circa 1500. Subsequently, anatomists da Carpi and Vesalius formally described the appendix in the mid-1500s. Soon thereafter, in 1554, Fernel described the first recorded case of disease of this organ: a 7-year-old girl with diarrhea was administered treatment with a large quince fruit, which obstructed the appendiceal lumen after it was ingested. She developed severe abdominal pain and died. Autopsy showed the quince fruit obstructing the appendiceal lumen, with resultant appendiceal necrosis and perforation, thereby resulting in the first description, postmortem, of what would later be known as “appendicitis.”

It was not until several centuries later that appendicitis was first diagnosed before autopsy and treated. Amyand is credited with performing the first
appendectomy in 1736, when he operated on a child with an inguinal hernia that had been complicated by the development of an enterocutaneous fistula. On exploration of the hernia sac, he discovered the appendix, which had been perforated by a pin, resulting in an appendicocutaneous fistula. As a result of his original description, an inguinal hernia sac containing the appendix carries Amyand’s eponym. Nearly 150 years passed before Lawson Tait in London performed the first successful transabdominal appendectomy for a gangrenous appendix in 1880. Less than a decade later, in 1886, Reginald Fitz of Harvard Medical School described the natural history of the inflamed appendix and coined the term “appendicitis.” In 1889, Charles McBurney of the Columbia College of Physicians and Surgeons in New York presented his series of cases of surgically treated appendicitis and, in doing so, described the anatomic landmark that now bears his name. McBurney’s point is the location of maximal tenderness “very exactly between an inch and a half and two inches from the anterior spinous process of the ilium on a straight line drawn from that process to the umbilicus.” In the 1890s, Sir Frederick Treves of London Hospital advocated conservative management of acute appendicitis followed by appendectomy after the infection had subsided; unfortunately, his youngest daughter developed perforated appendicitis and died from such treatment. The first laparoscopic appendectomy was performed by Kurt Semm in 1980. Refinement of the minimally invasive approach is the most recent of numerous advances in the diagnosis and treatment of appendicitis. Nonetheless, acute appendicitis continues to challenge surgeons to this day.

ANATOMY

Embryologically, the appendix and cecum develop as outpouchings of the caudal limb of the midgut loop in the sixth week of human development. By the fifth month, the appendix elongates into its vermiform shape. Containing all layers of the colonic wall, the appendix is, by definition, a true diverticulum. At birth, the appendix is located at the tip of the cecum. Because of unequal elongation of the lateral wall of the cecum, the adult appendix originates from the posteromedial wall of the cecum, caudal to the ileocecal valve. The adult appendix averages 9 cm in length, with its outside diameter ranging from 3 to 8 mm and its lumen ranging from 1 to 3 mm. The
base of the appendix is consistently found by tracing the teniae coli of the colon to their confluence at the base of the cecum. The appendiceal tip, however, can vary significantly in location (Fig. 41-1). Although usually located in the right lower quadrant (RLQ) or pelvis, the tip can occasionally reside in the left lower quadrant or right upper quadrant (RUQ).

**FIGURE 41-1** Anatomic variation in the position of the appendix. (1) Preileial; (2) postileal; (3) promontoric; (4) pelvic; (5) subcecal; (6) paracolic or prececal.

The arterial supply of the appendix comes from the appendicular branch of
the ileocolic artery, which originates posterior to the terminal ileum, enters the mesoappendix near the base of the appendix, and runs its course through to the tip of the appendix (Fig. 41-2). Lymphatic drainage flows to lymph nodes along the ileocolic artery.

**FIGURE 41-2** The appendix and its arterial supply.

**ACUTE APPENDICITIS**
Epidemiology

The incidence of acute appendicitis ranges from 8.6 to 11 cases per 10,000 person-years. The disease is slightly more common in males, although perforated cases have no gender predilection. In a lifetime, 8.6% of males and 6.7% of females can be expected to develop acute appendicitis. Young age is a risk factor; nearly 70% of patients are younger than 30 years of age when diagnosed with acute appendicitis. The highest incidence of appendicitis in males is in the 10- to 14-year-old age group (27.6 cases per 10,000 person-years), while the highest female incidence is in the 15- to 19-year-old age group (20.5 cases per 10,000 person-years). Overall, perforation occurs in 19% of cases of acute appendicitis. Perforated appendicitis has a bimodal distribution, with a predilection for patients at extremes of age. The ratio of perforated to nonperforated appendicitis is significantly higher among patients younger than 5 and older than 65 years, compared to those between 5 and 65 years of age. Although acute appendicitis is relatively uncommon in people older than 65 years, the elderly have perforated disease up to 50% of the time.

Etiology and Pathophysiology

The physiologic function of the appendix remains unknown, although some postulate it to be a microbial reservoir. Equally, the pathophysiology of the appendix in appendicitis is incompletely understood. Wangensteen and Dennis extensively studied the role of obstruction in appendicitis in the 1930s. Based on anatomic studies, he postulated that mucosal folds and a sphincter-like orientation of muscle fibers at the appendiceal orifice make the appendix susceptible to obstruction. As such, the pathophysiology of appendicitis is commonly believed to adhere to the following sequence of events: (1) Closed-loop obstruction caused by a fecalith (or other nidus, such as a calculus or neoplasm) leads to swelling of the mucosal and submucosal lymphoid tissue at the base of the appendix; (2) intraluminal pressure increases as the appendiceal mucosa secretes fluid against the fixed obstruction; (3) appendiceal wall pressure exceeds capillary pressure and causes mucosal ischemia; and (4) luminal bacterial overgrowth and translocation of bacteria across the appendiceal wall further result in
inflammation, edema, ischemia, and ultimately necrosis. If the appendix is not removed, perforation may ensue.

Although appendiceal obstruction is widely accepted as the primary cause of appendicitis, some evidence suggests that this may be only one of several possible mechanisms. First, some patients with a fecalith have a histologically normal appendix and, furthermore, the majority of patients with appendicitis show no evidence for a fecalith. Arnbjörnsson and Bengmark\textsuperscript{17} intraoperatively inspected the appendices of patients with suspected appendicitis. The intraluminal pressure of each appendix was measured prior to removal and found to be elevated in only 8 of 27 patients with nonperforated appendicitis. The authors did not observe signs of obstruction in the remaining patients with nonperforated appendicitis or those with a normal appendix. Taken together, these studies imply that obstruction is just one of the possible etiologies of acute appendicitis. Further mechanisms have yet to be completely elaborated.

Regardless of the role of obstruction as the inciting factor for appendicitis, it is a tenet of general surgery that, if left untreated, appendiceal inflammation will progress to necrosis and, ultimately, to perforation. In one study of the natural history of appendicitis, patients undergoing appendectomy for suspected appendicitis were queried about their duration of symptoms.\textsuperscript{18} Patients found to have nonperforated appendicitis reported an average duration of 22 hours of symptoms prior to presentation to the hospital, while those with perforated appendicitis reported an average of 57 hours. Similarly, in a study of over 1000 patients who underwent appendectomy for acute appendicitis, Ditillo and colleagues\textsuperscript{19} assessed the relationship between duration of symptoms and rate of perforation. Compared to the 6\% perforation rate among those with less than 12 hours of symptoms, patients with 48 to 71 hours of symptoms had a 33\% perforation rate and patients with greater than 71 hours of symptoms had a 39\% perforation rate.\textsuperscript{19}

However, the time course of this progression varies between patients. Among cases of perforated appendicitis, as many as 20\% present within 24 hours of the onset of symptoms.\textsuperscript{19} Although concern for perforation should be elevated when evaluating a patient with more than 24-hour duration of symptoms, the clinician must remember that perforation can also develop more rapidly. Importantly, this does not mean that surgeons are obliged to hastily proceed to an operation when appendicitis is suspected in order to
minimize the likelihood of perforation in exchange for a higher rate of misdiagnosis. Rather, Temple and colleagues\textsuperscript{18} demonstrated that patients with perforated appendicitis proceeded to surgery more rapidly than those with nonperforated appendicitis (6.5 vs 9 hours), but perforated patients had significantly longer prehospital symptoms (57 vs 22 hours). That is, longer duration of prehospital delay is the major contributor to perforation rather than delayed in-hospital diagnosis.\textsuperscript{20,21}

Some epidemiologic work highlights unsolved aspects of the mechanism of progression from nonperforated to perforated appendicitis. A study of US discharges in the National Hospital Discharge Survey notes that, although the incidence of nonperforated appendicitis has continued to decrease over time, the incidence of perforated appendicitis has slowly increased, despite the increasing and nearly pervasive availability of cross-sectional imaging and minimally invasive surgery.\textsuperscript{22} The authors suggest that this divergence in trends may indicate an underlying difference in pathophysiology between perforated and nonperforated appendicitis, rather than simply a difference in duration of disease.

**Diagnosis**

**PRESENTATION**

Although acute appendicitis is the most common surgically correctable cause of abdominal pain, its diagnosis remains challenging in many instances. Presenting signs and symptoms are variable and often initially subtle. Arriving at the correct diagnosis is essential, however, as a delay in diagnosis may allow progression to increasingly complex disease with concomitantly elevated morbidity and mortality. Conversely, incorrectly diagnosing appendicitis, although not catastrophic, subjects the patient to a potentially unnecessary operation.

The classic presentation of acute appendicitis begins with cramping, intermittent abdominal pain, thought to be due to obstruction of the appendiceal lumen, as nociceptors supplying the visceral peritoneum are stimulated by stretch. Classically, in 12 to 24 hours, the pain migrates to the RLQ as transmural inflammation of the appendix leads to inflammation of the peritoneal lining of the right lower abdomen. The character of the pain also changes from dull and colicky to sharp and constant. Movement or
Valsalva maneuver often worsens this pain, so that the patient typically desires to lie still; some patients describe pain with every bump in the car or ambulance ride to the hospital.

The prototypical patient with appendicitis initially endorses pain that is periumbilical or diffuse and difficult to localize. The onset of pain is typically followed shortly thereafter with nausea. Vomiting may or may not be present. If nausea and vomiting precede the pain, the astute clinician should consider another diagnosis, such as gastroenteritis. Upon detailed questioning, patients who have appendicitis commonly report anorexia, and appendicitis is unlikely in those with a normal appetite. Patients may report low-grade fever, while higher temperatures and shaking chills might again alert the surgeon to consider other diagnoses, including appendiceal perforation or nonappendiceal sources of abdominal pain.

**PHYSICAL EXAMINATION**

On inspection, patients with acute appendicitis appear mildly ill, feel warm to the touch, and have a slightly elevated pulse. They often lie still to avoid the irritation to the parietal peritoneum caused by movement. The surgeon should systematically examine the entire abdomen, starting in the left upper quadrant away from the patient’s described pain. Maximal tenderness is typically in the RLQ, at or near McBurney’s point, located one-third of the way from the anterior superior iliac spine to the umbilicus. This tenderness is often associated with localized muscle rigidity and signs of peritoneal inflammation, including rebound, shake, or tap tenderness. RLQ tenderness is one of the most specific of all signs of acute appendicitis. Its presence should always prompt diagnostic consideration of appendicitis, even in the absence of other signs and symptoms. Because of the various anatomic locations of the appendix, however, it is possible for the tenderness to be in the right flank, RUQ, suprapubic region, or left lower quadrant. Patients with a retrocecal or pelvic appendix may lack abdominal tenderness to palpation. In such cases, digital rectal examination can potentially be helpful to elicit right-sided pelvic tenderness. However, in general, digital rectal exam is an inaccurate assessment tool for diagnosing appendicitis.

Multiple physical exam signs contribute uniquely to the diagnosis of acute appendicitis. The Rovsing sign, or pain in the RLQ that occurs with release of applied pressure to the left lower quadrant, results from focal peritoneal
inflammation in the RLQ. Psoas sign, or pain with right hip flexion, can be seen with a retrocecal appendix due to inflammation adjacent to the iliopsoas muscle group. The obturator sign, or pain with internal rotation of the flexed right thigh, indicates inflammation adjacent to the obturator internus muscle in the pelvis.

However, many patients with acute appendicitis do not endorse the aforementioned typical history and physical examination. In practice, the surgeon is frequently reminded that the classic presentation of acute appendicitis is not universally present. For instance, the initial vague colicky pain may be overlooked or forgotten. When the pain becomes constant, it may localize to quadrants of the abdomen other than the RLQ due to alteration in appendiceal anatomy, as with late pregnancy or underlying malrotation. Among patients with a retrocecal appendix, the pain may not localize until generalized peritonitis from perforation occurs. Increased urinary or bowel frequency may occur due to appendiceal inflammation irritating the adjacent bladder or rectum. Because appendicitis is so common, a high index of suspicion for appendicitis is warranted in nearly all patients with abdominal pain. At the same time, because the differential diagnosis of appendicitis is extensive, patients should be queried about certain symptoms that may suggest an alternative diagnosis. Surgeons must also remember that a previous appendectomy does not definitively exclude the diagnosis of appendicitis, as “stump appendicitis” (appendicitis in the remaining appendiceal stump after appendectomy), although rare, has been described.25

**SYMPTOMS AND SIGNS OF PERFORATED APPENDICITIS**

When acute appendicitis has progressed to appendiceal perforation, other symptoms may be present. Patients will often endorse 2 or more days of abdominal pain. The pain usually localizes to the RLQ if the perforation has been walled off by surrounding intra-abdominal structures including the omentum, but it may be diffuse if generalized peritonitis ensues. The pain may become so severe that patients do not remember the antecedent colicky pain. A history of poor oral intake and dehydration may also be present.

In cases of perforated appendicitis, patients can look gravely ill. Patients with perforation often have rigors and high fevers. On physical examination, patients may appear flushed with dry mucous membranes. If a systemic
inflammatory response ensues, tachycardia and blood pressure depression will eventually occur in the absence of treatment. If the perforation has been walled off by surrounding structures to create an abscess or phlegmon, a mass may be palpable in the RLQ. Finally, if free intraperitoneal rupture has occurred, the patient can demonstrate signs of generalized peritonitis with diffuse rebound tenderness.

While most patients with perforated appendicitis present with symptoms related to the inflamed appendix itself or to a localized intraperitoneal abscess from perforation, other more rare presentations may occur. These are most likely to occur in the very young and very old, who may be unable to describe their symptoms and often present late in the course of their disease. On occasion, patients will present with bilious vomiting and obstipation due to a small bowel obstruction resulting from appendiceal perforation. Infectious complications can occur as well. A retroperitoneal abscess can form due to perforation of a retrocecal appendix. Alternatively, a hepatic abscess can form due to hematogenous seeding through the portal venous system. An intraperitoneal abscess may fistulize to the skin, resulting in an colocutaneous fistula. Finally, pylephlebitis (septic portal vein thrombosis) presents with high fevers and jaundice and can be confused with cholangitis; it is a rare dreaded complication of acute appendicitis and carries a high mortality.26

LABORATORY STUDIES

Laboratory studies contribute to the diagnosis of appendicitis, but no single test is definitive. A white blood cell (WBC) count is perhaps the most useful laboratory test. Typically, the WBC is slightly elevated in nonperforated appendicitis but may be quite elevated in the presence of perforation. The clinician must remember, however, that the WBC can be normal in patients with acute appendicitis, particularly in early cases. Although a late diagnostic sign, serial WBC measurements commonly demonstrate a rising value over time among patients with appendicitis.27 Urinalysis is performed to evaluate other potential causes for abdominal pain, specifically urinary tract infection and ureterolithiasis. Significant hematuria with colicky abdominal pain and the inability to find a comfortable resting position suggest the alternative diagnosis of ureterolithiasis. A urinary tract infection, on the other hand, is not uncommon in patients with appendicitis. It is not uncommon for the
urinalysis in a patient with appendicitis to show some degree of pyuria or hematuria due to inflammation of the ureter by the adjacent appendix. As such, its presence does not exclude the diagnosis of acute appendicitis, but it should be identified and treated.

In certain clinical situations, other laboratory tests are indicated. Measurement of serum liver enzymes and amylase can be helpful in diagnosing liver, gallbladder, or pancreatic disease for patients endorsing midabdominal or RUQ pain. Among women of childbearing age, the urine β-human chorionic gonadotropin should be checked to alert the clinician to the possibility of ectopic or concurrent pregnancy. Ectopic pregnancy is another cause of RLQ pain that demands emergent diagnosis and treatment. Concurrent pregnancy should be identified before a patient with suspected appendicitis is subjected to ionizing radiation from imaging studies or to general anesthesia.

**DIAGNOSTIC SCORES**

Diagnostic scoring systems have been developed in attempts to improve the diagnostic accuracy of acute appendicitis.\(^\text{28}\) The most prominent of those scores, developed by Alvarado,\(^\text{28}\) was based on a retrospective analysis of 305 patients with abdominal pain suspicious for appendicitis (Table 41-1). This scoring system assigns points for symptoms (migration of pain, anorexia or urine acetone, and nausea/emesis), physical signs (RLQ tenderness to palpation, rebound tenderness, and pyrexia), and laboratory values (leukocytosis and a left shift). One prospective study reported that an Alvarado score ≥7 in male patients or ≥9 in female patients was equivalent to computed tomography (CT) imaging consistent with acute appendicitis.\(^\text{29}\)

Although these scores can help guide clinical thinking, they do not markedly improve diagnostic accuracy.\(^\text{30}\) With the recent improvement in imaging studies, these scores have become increasingly marginalized.

<table>
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<th>TABLE 41-1: ALVARADO SCORING SYSTEM FOR ACUTE APPENDICITIS(^\text{28})</th>
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<td><strong>Symptoms</strong></td>
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<td>Migration of pain</td>
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<td>Anorexia or urine acetone</td>
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<td>Nausea/Emesis</td>
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<td><strong>Physical Signs</strong></td>
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<td>RLQ tenderness to palpation</td>
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<td><strong>Laboratory Values</strong></td>
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<td>Leukocytosis</td>
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Imaging Studies

The potential imaging modalities currently used for the diagnosis of acute appendicitis include ultrasound (US), CT, and magnetic resonance imaging (MRI). Of historic note, prior to the widespread use of modern imaging techniques, an RLQ fecalith (or appendicolith) on abdominal plain film was considered pathognomonic for acute appendicitis. However, identification of a fecalith on abdominal plain film is not a specific or sensitive sign for acute appendicitis. Teicher and colleagues\(^3^1\) reviewed the abdominal radiographs of 100 patients who underwent negative appendectomy and 100 patients who underwent appendectomy with pathologically proven appendicitis. Of those with appendicitis, 11% had an appendicolith on x-ray, compared to 3% of those without appendicitis. Similarly, an extensive review of appendectomy specimens at the Mayo Clinic\(^1^6\) showed that fecaliths or appendiceal calculi were present in 9% of patients with nonperforated appendicitis and 21% of those with perforated appendicitis. Fecaliths were also present in 7% of patients with suspected appendicitis who had a pathologically normal appendix and in 2% of patients who had an appendectomy for other reasons. These data suggest that plain abdominal radiographs are neither helpful nor cost-effective and, as such, are not recommended for the diagnosis of acute appendicitis. Plain radiographs may be indicated for evaluation of possible

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<td><strong>Symptom</strong></td>
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<tr>
<td>Migration of pain</td>
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<tr>
<td>Anorexia or urine acetone</td>
<td>1</td>
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<tr>
<td>Nausea/emesis</td>
<td>1</td>
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<tr>
<td><strong>Sign</strong></td>
<td></td>
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<tr>
<td>RLQ tenderness to palpation</td>
<td>2</td>
</tr>
<tr>
<td>Rebound tenderness</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia $\geq 37.3^\circ\text{C}$</td>
<td>1</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
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<tr>
<td>Leukocytosis</td>
<td>2</td>
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<td>Left shift</td>
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Abbreviation: RLQ, right lower quadrant.
perforated viscus, especially in certain patient populations such elderly patients with severe abdominal pain.

Abdominal ultrasonography is an important imaging modality for the diagnosis of acute appendicitis. A recent meta-analysis of 14 prospective studies showed US to have an overall sensitivity and specificity of 86% and 81%, respectively.\textsuperscript{32} Findings that suggest appendicitis include thickening of the appendiceal wall, loss of wall compressibility, increased echogenicity of the surrounding fat signifying inflammation, and loculated pericecal fluid (Fig. 41-3). The advantages of US include its widespread availability and the avoidance of ionizing radiation and the side effects of intravenous contrast, such as renal toxicity and allergic reactions. In addition, US (both abdominal and transvaginal) is particularly useful in assessing obstetric and gynecologic causes of abdominal pain in women of childbearing age. US is highly operator-dependent, however, and it is frequently unable to visualize the normal appendix.\textsuperscript{33} In the current epidemic of overweight and obesity in the United States, body habitus also limits the utility of US in the diagnosis of appendicitis, especially among patients with increasing body mass index (BMI).\textsuperscript{34}
FIGURE 41-3  Appendiceal ultrasound showing distended, noncompressible appendix measuring 1.7 cm in transverse dimension (>0.6 cm is abnormal). (Used with permission from M. Stephen Ledbetter, MD, MPH, Brigham and Women’s Hospital, Boston, MA.)

CT is the most frequently used imaging modality for the evaluation of acute appendicitis. CT benefits from a high diagnostic accuracy for appendicitis as well as visualization and diagnosis of many of the other causes of abdominal pain that can be confused with appendicitis. The radiographic findings of appendicitis on CT include a dilated (>6 mm), thick-walled appendix that does not fill with enteric contrast or air, as well as surrounding fat stranding to suggest inflammation (Fig. 41-4). In a meta-analysis of 12 prospective studies, CT demonstrated a sensitivity of 94% and a specificity of 95%. Appendicitis is highly unlikely if enteric contrast fills
the lumen of the appendix and no surrounding inflammation is present. However, the clinician must remember that a CT performed early in the course of appendicitis might not show the typical radiographic findings.

**FIGURE 41-4** Computed tomography of acute appendicitis. The *arrow* points to an enlarged, fluid-filled appendix with wall hyperemia that does not fill with oral contrast. The paucity of intra-abdominal fat limits identification of fat stranding. (Used with permission from M. Stephen Ledbetter, MD, MPH, Brigham and Women’s Hospital, Boston, MA.)

While CT imaging may rule out alternative diagnoses or assist in operative planning, it is important to note that CT imaging only reduces the rate of negative appendectomy among certain patients. Wagner and colleagues\(^ {36} \) conducted a review of over 1400 patients who underwent appendectomy for suspected acute appendicitis. The authors discovered that preoperative CT was associated with a lower rate of negative appendectomy only for adult female patients, but not for adult male patients or children.\(^ {36} \)

A number of prospective studies have compared the accuracy of CT and US in imaging the appendix (Table 41-2).\(^ {33,37,38} \) Balthazar and colleagues\(^ {37} \) performed CT and US on 100 consecutive patients with suspected appendicitis. The sensitivity of CT was considerably higher (96% for CT vs 76% for US), whereas the specificity was comparable (89% for CT vs 91% for US), yielding a higher accuracy for CT (94% for CT vs 83% for US). CT
was also able to provide an alternative diagnosis in more patients and was better able to visualize an abscess or phlegmon (Fig. 41-5). Horton and colleagues\textsuperscript{38} randomized patients with suspected appendicitis to either CT or US. Their findings echo those of Balthazar, with both CT and US having high specificity (100% for CT vs 90% for US), but CT demonstrating significantly higher sensitivity than US (97% for CT vs 76% for US). Yet another prospective study showed similar results, with CT having higher sensitivity (96% for CT vs 62% for US) and specificity (92% for CT vs 71% for US) than US\textsuperscript{33} and better ability to visualize other intra-abdominal pathology in the absence of appendicitis.

\textbf{FIGURE 41-5} Computed tomography of perforated appendix. Note retrocecal abscess (\textit{arrows}) with enhancing wall and periappendiceal fat stranding and adjacent cecal thickening (\textit{arrowhead}). (Used with permission from M. Stephen Ledbetter, MD, MPH, Brigham and Women’s Hospital, Boston, MA.)
TABLE 41-2: ACCURACY OF CT AND US FOR THE DIAGNOSIS OF ACUTE APPENDICITIS

<table>
<thead>
<tr>
<th>Author</th>
<th>Modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balthazar et al</td>
<td>CT</td>
<td>96</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>76</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>Horton et al</td>
<td>CT</td>
<td>97</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>76</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Wise et al</td>
<td>CT</td>
<td>96</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>62</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Terasawa et al (meta-analysis)</td>
<td>CT</td>
<td>94</td>
<td>95</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>86</td>
<td>81</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; NA, not applicable; US, ultrasound.

Taken together, these studies suggest an algorithm for evaluation of patients with suspected acute appendicitis. Patients with a history, physical examination, and laboratory studies consistent with appendicitis should undergo appendectomy based on clinical judgment. In those with an evaluation suggestive but not convincing for appendicitis, further imaging is warranted. In women of childbearing age, this should begin with a pelvic US to evaluate for ovarian pathology. For other patients, transabdominal US should be considered initially with a subsequent abdominopelvic CT scan if the diagnosis remains questionable or an intra-abdominal abscess/phlegmon requires better evaluation. Rectal contrast CT is rarely needed but can be employed to better visualize the appendix.\textsuperscript{33,35} Patients with a CT showing nonperforated appendicitis should undergo appendectomy. In many instances, patients with a normal CT do not require hospital admission. If symptoms persist, admission to the hospital for observation is warranted. Imaging modalities that avoid ionizing radiation may be preferentially used among children and pregnant patients, as discussed below.

DIFFERENTIAL DIAGNOSIS

Because many of its signs and symptoms are nonspecific, the differential diagnosis of acute appendicitis is extensive and includes both abdominal and nonabdominal sources of pain (Table 41-3). However, some diagnoses are more likely than others in certain settings. Meckel diverticulitis causes similar symptoms with the possible addition of episodic painless hematochezia but is relatively uncommon.\textsuperscript{39} Gastroenteritis is considerably
more common and should be expected when nausea and vomiting precede the abdominal pain or when diarrhea is a prominent symptom. Crohn’s disease affecting the terminal ileum may resemble appendicitis in its initial presentation, but on further questioning, the patient may describe a subacute course, including fever, weight loss, and pain.

**TABLE 41-3: DIFFERENTIAL DIAGNOSIS OF ACUTE APPENDICITIS**

**Gastrointestinal causes**
- Cecal diverticulitis
- Sigmoid diverticulitis
- Meckel diverticulitis
- Epiploic appendicitis
- Mesenteric adenitis
- Omental torsion
- Crohn’s disease
- Cecal carcinoma
- Appendiceal neoplasm
- Lymphoma
- Typhlitis
- Small bowel obstruction
- Perforated duodenal ulcer
- Internal hernia
- Intussusception
- Acute cholecystitis
- Hepatitis
- Pancreatitis

**Infectious causes**
- Infectious terminal ileitis (*Yersinia*, tuberculosis, or cytomegalovirus)
- Gastroenteritis
- Cytomegalovirus colitis

**Genitourinary causes**
- Pyelonephritis or perinephric abscess
Nephrolithiasis
Hydronephrosis
Urinary tract infection

**Nonabdominal causes**
Streptococcal pharyngitis
Lower lobe pneumonia
Rectus muscle hematoma

**In women**
Ovarian cyst (ruptured or not ruptured)
Corpus luteal cyst (ruptured or not ruptured)
Ovarian torsion
Endometriosis
Pelvic inflammatory disease
Tubo-ovarian abscess

**In pregnancy**
Ectopic pregnancy
Round ligament pain
Chorioamnionitis
Placental abruption
Preterm labor

In middle-aged and older adults, other inflammatory conditions should be considered, including gastric or duodenal ulcer (with symptoms from fluid tracking into the right paracolic gutter), cholecystitis, and pancreatitis. In addition, the symptoms of cecal or sigmoid diverticulitis overlap with those of acute appendicitis. Cecal diverticula, like the appendix, are true diverticula containing all layers of the intestinal wall. Cecal diverticulitis, intuitively, is similar in pathogenesis and presentation to appendicitis. Because a redundant, floppy sigmoid colon can extend to the right side of the abdomen, patients with sigmoid diverticulitis can sometimes present with RLQ pain. Those patients typically describe a more rapid progression to localized tenderness, as well as a prodrome of alteration in bowel habits. Malignancies can present with acute RLQ pain due to perforation of a cecal carcinoma or appendicitis caused by tumor obstructing the appendiceal orifice. Such patients will also
often have guaiac-positive stools, anemia, and a history of weight loss.

In women of childbearing years, diagnosing the underlying cause of RLQ pain can be even more difficult. In addition to the causes of RLQ pain mentioned above, young women can also have pain from obstetric and gynecologic etiologies such as ruptured ovarian cyst or follicle, ovarian torsion, ectopic pregnancy, acute salpingitis, and tubo-ovarian abscess. A complete history including recent menstrual history, as well as pelvic examination, can be helpful in differentiating these causes of pain from acute appendicitis. Nonetheless, appendicitis can be difficult to diagnose in this patient population, and higher rates of misdiagnosis have been described in women of childbearing age. 40

SPECIAL CONSIDERATIONS

Children

In the pediatric population, appendicitis most commonly afflicts children age 10 to 19 years, with an overall incidence of approximately 20 cases per 10,000 person-years. 12 By age 20, approximately 4% of children and adolescents will have undergone an appendectomy. 41 Among those younger than 20, infants age 0 to 4 have the lowest incidence of appendicitis (2 cases per 10,000 person-years), but up to two-thirds will present with perforation. 42 Perforation is disproportionately common because infants often present later in their disease course due to the difficulty inherent in obtaining an accurate history. The diagnosis is further complicated by diseases of childhood that can mimic appendicitis. For instance, mesenteric adenitis, or inflammation of the mesenteric lymph nodes, can present with fever and RLQ pain. Streptococcal pharyngitis and bacterial meningitis can also present with fever, nausea, and abdominal pain. These diagnoses and others including ovarian cysts, ovarian torsion, urinary tract infection, pelvic inflammatory disease, and complications of a Meckel diverticulum should be considered when evaluating children or adolescents for suspected appendicitis.

For the many children with an equivocal history, physical examination, and laboratory data, imaging with US is the preferred initial study. 43 US lacks ionizing radiation, does not require contrast or sedation, and is relatively
inexpensive. Unfortunately, however, ultrasonography is operator dependent. A meta-analysis by Doria and colleagues\textsuperscript{44} of over 7000 patients documents a pooled sensitivity and specificity of 88% (95% confidence interval [CI], 86%-90%) and 94% (95% CI, 92%-95%), respectively, for the sonographic diagnosis of appendicitis. An important determinant in the diagnostic success of US is BMI of the child. The sensitivity of US has been reported to be 76% for children with a BMI below 25, but as low as 37% for children with a BMI of greater than 25. US had 82% sensitivity for appendicitis in one study in which the patient population had a mean BMI of 17.\textsuperscript{45-47}

When US results are indeterminate, cross-sectional imaging with MRI or CT can help identify intra-abdominal pathology. MRI warrants consideration as the preferred second-line imaging test among children with suspected appendicitis, provided that the modality and its interpretation are institutionally available, the child is clinically stable, and the child is of old enough age to tolerate lying still for a relatively lengthy study. MRI lacks ionizing radiation and has at least equivalent sensitivity and specificity to CT. In a single-institution study of 510 MRIs, Kulaylat and colleagues\textsuperscript{48} reported both a sensitivity and specificity of 97% for the diagnosis of acute appendicitis. The median imaging duration was 11 minutes. In comparison, CT has the benefits of nearly universal availability, ease of interpretation, and rapid examination. However, ionizing radiation from CT in childhood theoretically causes a small increase in the lifetime risk of certain cancers.\textsuperscript{49} Based on estimated radiation exposure from a CT scan, studies have hypothesized that a 1-year-old and 15-year-old would theoretically develop a 0.18% and 0.11% lifetime risk, respectively, of fatal radiation-induced malignancy following a CT scan.\textsuperscript{45} A recent study by Pearce and colleagues\textsuperscript{50} studied the long-term outcomes of patients under age 22 who underwent CT examination between 1985 and 2002. The authors reported one excess occurrence of leukemia and one excess occurrence of a brain tumor per 10,000 head CTs. Despite this association between ionizing radiation and malignancy, the retrospective nature of the available research and the small magnitude of the absolute risk of malignancy (given the low overall rate) should be emphasized. Therefore, clinicians should consider the risks and benefits of MRI and CT, and efforts should be directed toward reducing radiation dose when imaging children.\textsuperscript{51}

There is substantial variability in usage of imaging modalities. For
example, in a study by Rice-Townsend and colleagues of data from the Pediatric Health Information System database, hospital utilization of preoperative imaging with CT or US ranged from 21% to 73%.\textsuperscript{52} In efforts to systematically reduce such variation, Rangel and colleagues proposed an algorithm to diminish the utilization of CT imaging for children with suspected appendicitis. Incorporating laboratory tests and US findings, the rate of CT utilization was substantially decreased, from 21% to 4%, with an unchanged rate of negative appendectomy.\textsuperscript{53}

**Elderly**

Although appendicitis is more common in younger age groups, it is an important cause of abdominal pain in the elderly. Perhaps because of a diminished inflammatory response, the elderly can present with less impressive symptoms and physical signs, longer duration of symptoms, and decreased leukocytosis compared to younger patients.\textsuperscript{54} Perforation is thus more common, occurring in as many as 50% of patients older than 65.\textsuperscript{12} These patients may have cardiac, pulmonary, renal, and other comorbidities, resulting in considerable potential morbidity and mortality from perforation. In one series, the mortality from perforated appendicitis in patients older than 80 was 21%.\textsuperscript{55} These factors argue that RLQ pain in elderly patients must be efficiently investigated. Because of the multiple other possible causes of abdominal pain in this patient population (including malignancy, diverticulitis, and perforated peptic ulcer disease), prompt CT scan should be considered when the diagnosis is in question.

**Pregnancy**

The diagnosis of acute appendicitis in the pregnant patient can be particularly challenging, as nausea, anorexia, and abdominal pain may be symptoms of appendicitis, abnormal pregnancy, and normal pregnancy. The differential diagnosis of appendicitis includes not only the conditions possible in nonpregnant women but also certain conditions specific to pregnancy: ectopic pregnancy, chorioamnionitis, preterm labor, placental abruption, and round ligament pain. In addition, the gravid uterus can displace the abdominal viscera, shifting the location of the appendix cephalad from the RLQ.
Appendicitis affects 1 in every 1400 pregnant women.\textsuperscript{56} It can occur in any trimester, with perhaps a slight increase in frequency during the second trimester.\textsuperscript{57} Perforation is most common in the third trimester, potentially resulting from a longer duration from the onset of symptoms to operation.\textsuperscript{57}

In the first and early second trimesters, the presentation of appendicitis is similar to that seen in nonpregnant women. In the third trimester, women may not present with RLQ pain due to cephalad displacement of the appendix by the gravid uterus. Baer and colleagues performed barium enemas on normal pregnant women and found the appendix to migrate superiorly toward the RUQ in later stages of pregnancy.\textsuperscript{58} Their findings suggest that appendicitis may present with RUQ or flank pain in late pregnancy. Two retrospective studies note that symptoms do not always reflect this cephalad displacement, however. Even in the third trimester, pain and tenderness are more common in the right lower quadrant than the RUQ.\textsuperscript{56}

Several studies highlight the difficulty of clinically diagnosing a pregnant patient with appendicitis. Brown and colleagues\textsuperscript{59} reviewed case-control studies that defined the relationship between preoperative presentation and the postoperative diagnosis of appendicitis in pregnant patients. Although patients presented with RUQ pain, RLQ pain, and fevers, only nausea, vomiting, and peritonitis were found to significantly correlate with the diagnosis of appendicitis. Furthermore, laboratory values are altered in the setting of pregnancy, and leukocytosis (including with a neutrophilic predominance) can be a normal finding.\textsuperscript{60}

Given the challenge of clinically diagnosing appendicitis in pregnancy, imaging is critical. US is accurate in pregnancy\textsuperscript{61} and is a useful radiologic study because it has no known adverse fetal effects.\textsuperscript{62} However, nonvisualization of the appendix is a frequent problem, especially in increasingly advanced gestations.\textsuperscript{63} In the setting of an US equivocal for appendicitis, MRI is an excellent modality. Like US, to date, no adverse effects of MRI on the developing fetus have been reported.\textsuperscript{64}

In a retrospective, multicenter study of 709 pregnant women with abdominal pain who underwent MRI for the evaluation of acute appendicitis, 66 (9%) had MRI findings consistent with appendicitis. The authors report sensitivity and specificity rates of 97% and 99%, respectively.\textsuperscript{65} Gadolinium should be avoided due to potential for teratogenicity. If MRI is unavailable or will cause an extreme delay in management, CT imaging of pregnant patients
with suspected appendicitis can and should be performed. The risk of radiation should be weighed against the risk of spontaneous abortion from an unnecessary laparotomy or from undiagnosed appendicitis progressing to perforation. Although ionizing radiation has risks to the fetus, the radiation from a typical abdominopelvic CT is below the threshold of 5 rad (50 mGy) at which teratogenic effects are seen. Furthermore, CT imaging protocols can be modified to reduce the amount of fetal radiation, without impacting diagnostic value.

The pregnant patient should proceed directly to appendectomy if appendicitis is suspected. A normal appendix is not an uncommon finding, as negative appendectomy has been reported in approximately one-third of cases due to the difficulty of diagnosis in this population. Negative appendectomy should not be considered an error in management, because the risk to the fetus varies directly with the severity and progression of appendicitis. In a large California inpatient database, the fetal loss rate after negative appendectomy was 4%. However, fetal mortality was 2% to 5% in cases of nonperforated appendicitis and 6% to 35% in cases of perforated appendicitis. These data warrant an expedited approach to appendectomy that favors operation.

As laparoscopic appendectomy has become increasingly popular, the technique has been adapted to appendectomy in pregnancy. Pregnancy can increase the complexity of the procedure, as the gravid uterus can make laparoscopic visualization difficult, particularly if the appendix is located in the pelvis. In addition, carbon dioxide insufflation of the abdomen results in fetal hypercarbia and decreased placental blood flow, the effects of which have not been completely studied. A meta-analysis including 11 studies from 1990 to 2011 with 3415 patients estimated a 91% higher relative risk of fetal loss in the laparoscopic group compared with the open appendectomy group. However, a more recent retrospective review from 2009 directly comparing laparoscopic to open appendectomy in 42 pregnant women found no intra- or postoperative complications in either group and 1 fetal loss in both groups. Given the large time frame and retrospective nature of included studies in the aforementioned meta-analysis, the conclusions drawn from this synthesis are limited. Caution should be exercised when selecting surgical approach to appendectomy during pregnancy. Furthermore, certain risk-minimizing measures should be taken, such as limiting the degree of
pneumoperitoneum. After uncomplicated appendectomy, there do not appear to be any lasting effects on child development. Choi and colleagues prospectively studied pregnant women who underwent appendectomy. Of 29 patients who delivered without complication (1 fetal death occurred due to extreme prematurity) and completed a detailed study survey of developmental milestones, none indicated developmental delay for their child, with a mean follow-up time of nearly 4 years.

**Immunocompromise**

The immunocompromised state alters the normal response to acute infection and wound healing. Appendicitis must be considered among those with abdominal pain who have undergone organ transplantation, are receiving chemotherapy, have a hematologic malignancy, or have decreased CD4 cell counts due to infection with the human immunodeficiency virus (HIV). The differential diagnosis of abdominal pain in the immunosuppressed population is broad and includes hepatitis, pancreatitis (from medications or cytomegalovirus infection), acalculous cholecystitis, intra-abdominal opportunistic infections (cytomegalovirus colitis or mycobacterial ileitis), secondary malignancies (lymphoma or Kaposi sarcoma), graft-versus-host disease, and typhlitis. This broad differential diagnosis often results in delay in diagnosis and late presentation to surgical evaluation, at which time perforation may be more likely.

Appendicitis in patients with HIV and acquired immunodeficiency syndrome (AIDS) presents unique challenges. Abdominal pain is not an uncommon symptom in these patients, making differentiation between surgical and nonsurgical causes difficult. Nonetheless, immunocompromised patients with appendicitis present with symptoms similar to those of the general population, including RLQ pain, nausea, and anorexia. Fever and WBC may not be helpful in this population given the underlying poor immune response. Therefore, imaging studies, particularly CT, have been supported by some authors. There is no specific contraindication to operation in immunocompromised patients. Once diagnosed with appendicitis, appendectomy should be performed promptly.

**TREATMENT**
Nonoperative Management

Appendectomy was one of the first intra-abdominal operations performed, and appendicitis has since been a surgically treated disease. Historically, Treves was an advocate of early nonoperative management of acute appendicitis, even prior to the advent of antibiotics. In the postantibiotic era, Coldrey presented his retrospective series of 471 patients with appendicitis treated with antibiotics. This treatment failed in at least 57 patients, with 48 requiring appendectomy and 9 requiring drainage of an appendiceal abscess. Decades after this 1959 study, interest in nonoperative management (NOM) has reemerged, based on the results of several randomized controlled trials. NOM is currently a topic of controversy in the contemporary management of acute appendicitis.

Recent data suggest that NOM with intravenous antibiotics may present an alternative to appendectomy. This management strategy parallels the treatment of sigmoid diverticulitis and is based on work suggesting that nonperforated and perforated appendicitis are distinct diseases. Potential benefits of NOM derive from the upfront avoidance of an invasive procedure, which must be weighed against the risk of immediate progression of disease as well as the long-term risk of recurrent appendicitis. Given the association between appendicolith and complicated appendicitis, patients with this imaging finding should not undergo NOM. Similarly, these data on NOM do not necessarily apply to other high-risk patients, such as pregnant patients, the immunosuppressed, and the elderly. On the other hand, antibiotic treatment is a useful temporizing measure in environments with no surgical capabilities such as in space flight and submarine travel. Of note, early data suggest feasibility of NOM among children with acute appendicitis. A recent prospective, nonrandomized cohort study was conducted of 102 children 7 to 17 years of age with suspected uncomplicated acute appendicitis who were offered the choice of NOM and appendectomy. Among children who underwent NOM, the 1-year rate of appendectomy (ie, 1-year failure rate of NOM) was 24%. Potential benefits of NOM in the pediatric population were found to be fewer disability days and lower health care costs related to treatment of appendicitis at 1 year after diagnosis, despite longer initial length of hospital stay. There are several important issues to highlight when considering NOM.
First, laparoscopic (or open) appendectomy for uncomplicated acute appendicitis is a safe procedure, performed with very low levels of complication. Second, recurrence rates after NOM can be as high as 35%. In the recent Appendicitis Acuta (APPAC) study (described below), the recurrence rate of 27% exceeded the predefined threshold of an unacceptably high rate of recurrent appendicitis. In addition, imaging alone has a substantial false-negative rate for diagnosing perforated appendicitis. For example, in a 2011 trial by Vons and colleagues, 18% of patients who underwent appendectomy were unexpectedly found to have perforated appendicitis and peritonitis at the time of operation. Finally, NOM does not assess the presence of appendiceal neoplasm, which is discovered in as many as 1.5% of appendectomy specimens.

An early randomized controlled trial, performed by Eriksson and associates, first sought to evaluate the comparative effectiveness of NOM and appendectomy in 1995. The authors randomized 40 adults with presumed appendicitis to appendectomy or 10 days of intravenous and oral antibiotics. The results included a high rate of recurrent appendicitis after NOM. Eight (40%) of the 20 patients in the antibiotic group required appendectomy within 1 year: 1 patient for perforation within 12 hours of randomization and another 7 for recurrent appendicitis (1 of whom had perforation).

Since then, several other randomized controlled trials have addressed this same question. Table 41-4 displays the characteristics of 6 important randomized trials comparing the effectiveness of appendectomy and NOM. These data generally suggest fewer workdays lost with NOM and decreased duration and severity of abdominal pain. Initial cost may also be decreased with NOM, although long-term cost in the setting of recurrence and the need for close follow-up is challenging to define. In contradistinction, length of hospital stay tended to be lower with appendectomy. Neoplasm was detected after 0.5% to 1.5% of appendectomies. Recurrence rates after NOM ranged from 8% to 32%. This is consistent with a recent meta-analysis, in which the likelihood of failure was 23%.

| TABLE 41-4: STUDIES COMPARING NONOPERATIVE AND OPERATIVE MANAGEMENT OF ACUTE APPENDICITIS |
The most recent and largest to date randomized controlled trial was a noninferiority study by Salminen and colleagues. The APPAC trial was performed in 6 Finnish hospitals between 2009 and 2012. The researchers evaluated the effectiveness of antibiotic therapy (intravenous ertapenem for 3 days followed by oral levofloxacin and metronidazole for 7 days) versus open appendectomy (laparoscopic appendectomy was performed only 5% of the time) as the primary treatment for uncomplicated acute appendicitis among nonpregnant patients age 18 to 60 years. Patients with evidence of fecaliths, perforation, abscess, or tumor on CT imaging were excluded. Among patients randomized to NOM, the primary end point was need for appendectomy and recurrent appendicitis during 1-year of follow-up. Based on existing literature, the threshold for noninferiority was set at 24%. There were 273 and 257 patients randomized to appendectomy and NOM, respectively. Appropriate management strategy 99.6% of the time. In the NOM cohort, 27.3% of patients required an appendectomy within the first year of follow-up, exceeding the a priori threshold for noninferiority. Those with recurrent appendicitis underwent appendectomy at a median of 102 days after initial treatment. The complication rate after appendectomy for recurrent appendicitis in the NOM cohort was relatively low at 7%, compared to a complication rate of 20% in the appendectomy cohort. While this difference was statistically significant, many complications were minor, including superficial surgical site infection and pain-related symptoms. Appendiceal neoplasms were intraoperatively discovered in 1.5% of patients in the appendectomy cohort.

In summary, currently available data show a moderately high rate of

<table>
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<tr>
<th>Author and Year</th>
<th>No. (NOM, surgery)</th>
<th>Recurrence Rate (NOM only)</th>
<th>Cost</th>
<th>LOS</th>
<th>Duration of Abdominal Pain</th>
<th>Neoplasm (surgery only)</th>
<th>Workdays Lost</th>
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<td>Salminen et al.82 2016</td>
<td>257, 273</td>
<td>27%</td>
<td>NR</td>
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<td>Favors NOM</td>
<td>1.5%</td>
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<tr>
<td>Vos et al.77 2011</td>
<td>123, 120</td>
<td>32%</td>
<td>NR</td>
<td>Similar</td>
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<td>Similar</td>
</tr>
<tr>
<td>Turhan et al.88 2009</td>
<td>107, 183</td>
<td>8%</td>
<td>Favors NOM</td>
<td>Favors surgery</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hansson et al.85 2009</td>
<td>202, 167</td>
<td>14%</td>
<td>Favors NOM</td>
<td>Similar</td>
<td>Favors NOM</td>
<td>1/167 and 1/202</td>
<td>Favors NOM</td>
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<tr>
<td>Styrud et al.86 2006</td>
<td>128, 124</td>
<td>15% (1-year)</td>
<td>NR</td>
<td>Similar</td>
<td>NR</td>
<td>0%</td>
<td>Similar</td>
</tr>
<tr>
<td>Eriksson and Granström81 1995</td>
<td>20, 20</td>
<td>35%</td>
<td>NR</td>
<td>NR</td>
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<td>0%</td>
<td>NR</td>
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</tbody>
</table>

Abbreviations: LOS, length of hospital stay; NOM, nonoperative management; NR, not reported.
recurrence of appendicitis with NOM and a small but important risk of malignancy. As such, for the majority of patients with uncomplicated acute appendicitis, laparoscopic (or open) appendectomy should be considered the gold standard treatment, while NOM may be offered on a case-by-case basis in certain circumstances.

**Preoperative Preparation**

When the decision is made to perform an appendectomy for acute appendicitis, the patient should proceed to the operating room with little delay to minimize the chance of progression to perforation. While in-hospital progression to perforation is rare and most cases of appendiceal perforation occur prior to surgical evaluation, the operation should nevertheless be expedited.\(^{20,21}\) Patients with appendicitis may be dehydrated from fever and poor oral intake. Intravenous fluids should be infused, and vital signs including urine output should be closely monitored. Markedly dehydrated patients may require a Foley catheter to ensure accurate urine output monitoring. Severe electrolyte abnormalities are uncommon with nonperforated appendicitis, as vomiting and fever have typically been present for 24 hours or less but may be significant in cases of perforation. Any electrolyte derangements should be corrected prior to the induction of general anesthesia.

Intravenous broad-spectrum antibiotics have been shown to significantly reduce the incidence of postoperative wound infection and intra-abdominal abscess, including after negative appendectomy.\(^{41}\) Antibiotics should be administered at the time of diagnosis and re-dosed appropriately. The typical flora of the appendix resembles that of the colon and includes gram-negative aerobes (primarily *Escherichia coli*) and anaerobes (*Bacteroides* species). No standardized antibiotic regimen exists. Acceptable options include a second-generation cephalosporin or a combination of antibiotics directed at gram-negative bacteria and anaerobes, tailored to institutional antibiogram. In nonperforated appendicitis, a single preoperative dose of cefoxitin suffices.\(^{87}\) In cases of perforation, an antibiotic course of at least 4 days after source control is obtained is advocated, in accordance with recent findings from the randomized controlled Study to Optimize Peritoneal Infection Therapy (STOP-IT).\(^{88}\)
Laparoscopic Versus Open Appendectomy

Open appendectomy (OA) has been the standard of care for the surgical management of acute appendicitis since Amyand performed the first appendectomy in 1736. Little changed in the surgical management of this disease until Semm developed the laparoscopic appendectomy (LA) in 1980. Over the ensuing decades, laparoscopy has increasingly taken hold as the preferred approach to appendectomy. In an analysis of the Nationwide Inpatient Sample, Masoomi and colleagues documented an increase in the use of laparoscopy for appendectomy over the past decade, from 43% in 2004 to 75% in 2011.

Numerous randomized controlled trials have compared these 2 surgical approaches, sometimes with conflicting results. Meta-analyses and systematic reviews have combined these studies to address the controversy (Table 41-5). These meta-analyses have similar findings, which can be summarized as follows: (1) OA can be performed more quickly; (2) LA patients have less postoperative pain and reduced narcotic requirements; (3) there is a trend toward reduced length of stay with LA; (4) LA patients have fewer wound infections; (5) OA patients develop fewer intra-abdominal abscesses; (6) LA patients return to work more quickly; (7) operating room and hospital costs are decreased with OA; and (8) societal costs may be decreased with LA. Based on the available data, one cannot definitively recommend either OA or LA over the other.

TABLE 41-5: LAPAROSCOPIC VERSUS OPEN APPENDECTOMY
Laparoscopic appendectomy may be especially advisable for certain patient populations, including for women of childbearing age, obese patients, and the elderly. Among women of childbearing age, obstetric and gynecologic pathology may be clinically indistinguishable from appendicitis, and a normal appendix is found in more than 40% of patients with suspected appendicitis. However, when a normal appendix was discovered, gynecologic pathology was found in 73% of women explored laparoscopically but only 17% of women who had an OA. Among such patients with uncertain diagnosis, laparoscopy can thus be both diagnostic and therapeutic, avoiding a laparotomy if nonappendiceal pathology is found. Additionally, laparoscopy warrants consideration among obese patients, for whom open dissection is more technically challenging. In a National Surgical Quality Improvement Program (NSQIP) study of obese patients undergoing appendectomy, Mason and colleagues reported a 57% reduction in morbidity with laparoscopy, compared to the open approach, after adjusting for preoperative risk factors. For the elderly, LA was found to confer lower mortality (0.4% vs 2.1%) for uncomplicated appendicitis and a less complicated postoperative course (shorter length of hospital stay and higher rate of discharge home) for perforated appendicitis. Finally, among children, Esposito and colleagues conducted a literature review, which

<table>
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<th>Favors Laparoscopy</th>
<th>Favors Open</th>
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<td>Diagnosis of other conditions</td>
<td>Shorter operating room time</td>
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<tr>
<td>Decreased pain and lower narcotic requirement</td>
<td>Decreased operating room costs</td>
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<td>Decreased number of overall surgical site infections</td>
<td>Decreased number of intra-abdominal abscesses</td>
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<td>Decreased length of stay</td>
<td>Decreased hospital costs</td>
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<td>More rapid return to usual activities</td>
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<td>Decreased societal cost</td>
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revealed a lower incidence of surgical site infection, lower analgesic use, and more rapid recovery with laparoscopic, compared to open, appendectomy. Operative time was longer with laparoscopy than laparotomy for complicated appendicitis, but not for uncomplicated appendicitis. Ultimately, the decision of surgical approach to appendectomy should depend on patient factors and surgeon comfort with the technique.

**Laparoscopic Appendectomy**

Multiple port placements for LA exist. The authors use a three-port technique, with an umbilical port, a suprapubic port, and a left lower quadrant port (alternatively, an RLQ port could be used in the place of the latter). Although the third port can be placed in either the left lower quadrant or RLQ, we prefer the left lower quadrant. This follows the laparoscopic principle of triangulation, such that the port locations direct the camera and instruments toward the RLQ for optimal visualization of the appendix.

The patient is positioned supine on the operating room table with the left arm tucked to allow room for both the surgeon and assistant (Fig. 41-6). The video monitor is placed at the patient’s right side and, once pneumoperitoneum is performed, the surgeon and assistant both stand on the patient’s left. Prior to incision, a nasogastric tube and a Foley catheter can be placed to decompress the stomach and urinary bladder. A Foley catheter can be avoided if a reliable patient urinates immediately prior to entering the operating room. A 1- to 2-cm vertical or transverse incision is made just inferior to the umbilicus and carried down to the midline fascia. A 12-mm trocar is placed using either Hasson or Veress technique, depending on surgeon preference. After insufflation of the abdomen and inspection through the umbilical port, a 5-mm suprapubic port is placed in the midline, taking care to avoid injury to the bladder. Next, a 5-mm port is placed in the left lower quadrant. These port sites typically provide excellent cosmesis postoperatively due to their small size and peripheral location on the abdomen.
FIGURE 41-6 Laparoscopic appendectomy technique. A. Patient positioning, B. Port placement, C. Creation of mesoappendix window, and D. Transection of the appendix.

A 5-mm, 30-degree laparoscope is inserted through the left lower quadrant trocar. Placing the laparoscope in the left lower quadrant allows triangulation of the appendix in the RLQ by instruments placed through the 2 midline trocars. The surgeon operates the 2 dissecting instruments and the assistant operates the laparoscope. The appendix is identified at the base of the cecum at the confluence of the teniae coli. Any adhesions to surrounding structures can be lysed with a combination of blunt and sharp dissection supplemented with electrosurgery. If a retrocecal appendix is encountered, division of the
lateral peritoneal attachments of the cecum to the abdominal wall often improves visualization. Care must be taken to avoid injury to underlying retroperitoneal structures, specifically the right ureter and iliac vessels. The appendix or mesoappendix can be gently grasped with a Babcock clamp placed through the suprapubic port and retracted anteriorly. A dissecting forceps placed through the umbilical port creates a window in the mesoappendix at the appendiceal base. Caution should be taken not to injure the appendiceal artery during this maneuver, the risk of which can be reduced by dissecting close to the appendiceal base and out of the mesoappendix. The base of the appendix should be adequately dissected so that it can be divided without leaving a significant stump. The appendix should be divided at the confluence of the appendix and cecum, or just onto the cecal wall, to avoid the possibility of stump appendicitis or mucocele (see Fig. 41-6).

The appendix can be removed in a retrograde fashion, first dividing the appendix, followed by division of the mesoappendix. A laparoscopic gastrointestinal anastomosis stapler is placed through the umbilical port and fired across the appendiceal base. After reloading, the stapler is again inserted through the umbilical port and placed across the mesoappendix, which is also divided with firing of the stapler. Alternatively, the appendix can be secured using an Endoloop (Ethicon, Endo-Surgery, Cincinnati, OH) and the mesoappendix secured with Endoloop, clips or an electrosurgery device. If desired, the appendix can be removed antegrade by first dividing the mesoappendix prior to directing attention to the base. The appendix should be placed in a retrieval bag and removed through the umbilical port site to minimize the risk of wound infection. The operative field is inspected for hemostasis and can be irrigated with saline, although irrigation is typically not necessary. Finally, the fascial defect at the umbilicus is closed with absorbable 0 suture, and all skin incisions are closed with fine subcuticular absorbable suture. For nonperforated appendicitis, no further antibiotics are required.

Open Appendectomy

If OA is chosen, the surgeon must then decide on the location and type of incision. The patient should be reexamined after the induction of general anesthesia, which enables deep palpation of the abdomen. If a mass representing the inflamed appendix can be palpated, the incision can be
centered at that location. If no appendiceal mass is detected, the incision should be centered over McBurney’s point, one-third of the distance from the anterior superior iliac spine to the umbilicus. A curvilinear McBurney’s incision is made in a natural skin fold to avoid tension on the closure. It is important not to make the incision too medial or too lateral. An incision placed too medial opens onto the anterior rectus sheath, rather than the desired oblique muscles, while an incision placed too lateral may be lateral to the peritoneal cavity.

The operation proceeds as McBurney first described it in 1894.\(^{101}\) The incision extends through the subcutaneous tissue, exposing the aponeurosis of the external oblique muscle, which is divided, either sharply or with electrosurgery, in the direction of its fibers (Fig. 41-7). A muscle-splitting technique is typically used, in which the external oblique, internal oblique, and transversus abdominis muscles are separated along the orientation of their muscle fibers. The peritoneum is thus exposed, grasped with forceps, and opened sharply along the orientation of the incision, taking care not to injure the underlying abdominal contents. Hemostat clamps can be placed on the peritoneum to facilitate its identification at the time of wound closure. Cloudy fluid may be encountered on entering the peritoneum. Although some advocate bacterial culture of the peritoneal fluid, studies show that this superfluous practice neither helps direct the antibiotic regimen\(^{102}\) nor reduces infectious complications.\(^{103}\)
With a correctly placed incision, the cecum will be visible at the base of the wound. The incision should be explored with a finger in an attempt to locate the appendix. If the appendix is palpable and free from surrounding structures, it can be delivered through the incision. Frequently, the appendix is palpable, but adherent to surrounding structures. Filmy adhesions can be divided using blunt dissection, but thicker adhesions should be divided under direct vision. The cecum can be partially delivered through the incision to provide better exposure of the appendix. If necessary to further improve exposure, the incision can be extended medially by partially dividing the rectus muscle or laterally by further dividing the oblique and transversus
abdominis muscles. If the nonpalpable appendix cannot be visualized, it can be located by following the teniae coli of the cecum to the cecal base, from which the appendix invariably originates. Once located, the appendix is delivered through the incision. Grasping the mesoappendix with a Babcock clamp can sometimes facilitate this maneuver.

The arterial supply to the appendix, which runs in the mesoappendix, is now clamped, ligated with 3-0 silk suture, and divided. This is usually performed in an antegrade fashion, from the appendiceal tip toward the base. As in the laparoscopic approach, adequate dissection is necessary to ensure that the entire appendix can be removed without leaving an excessively long appendiceal stump, thereby allowing the potential for stump appendicitis.

In excising the appendix, the surgeon must decide whether or not to invert the appendiceal stump. Traditionally, the appendix had been ligated and divided and its stump inverted with a purse-string suture for the theoretical purpose of avoiding bacterial contamination of the peritoneum and subsequent adhesion formation. However, prospective studies show no advantage to appendiceal stump inversion. In one such study, 735 appendectomy patients were randomly assigned to ligation plus inversion or simple ligation of the appendiceal stump. There was no difference between the 2 groups in the incidence of wound infection or adhesion formation, and operating time was shorter in the simple ligation group. Inversion may also have the deleterious effect of deforming the cecal wall, which could be misinterpreted as a cecal mass on future contrast radiographs. Furthermore, the long-standing notion that stump inversion reduces postoperative adhesions was discredited by Street and colleagues. In their analysis, postoperative adhesions requiring operation were significantly increased in the inversion group.

To divide the appendix, the surgeon can use either suture ligation or a gastrointestinal stapler. For ligation, 2 hemostat clamps are placed at the base of the appendix. The clamp closest to the cecum is removed, having crushed the appendix at that site. Two heavy, absorbable sutures such as 0 chromic gut are used to doubly ligate the appendix, and the appendix is subsequently divided proximal to the second clamp. The exposed mucosa of the appendiceal stump can be cauterized to minimize the theoretical risk of postoperative mucocele, although no data exist to support this. If appendiceal stump inversion is chosen, a seromuscular purse-string 3-0 silk suture is
placed in the cecum around the appendiceal base after ligation but prior to division of the appendix. The purse-string suture should be placed approximately 1 cm from the base of the appendix, as placing it too close to the appendix makes stump inversion difficult. After the appendix is divided, the purse-string suture is tightened and tied while the assistant uses forceps to invaginate the appendiceal stump. Alternatively, the appendix can be divided at its base using a TA-30 stapler. Again, the stump need not be inverted, but can be if desired, using interrupted Lembert sutures with 3-0 silk suture. No matter how the appendix is divided, the residual appendiceal stump should be no longer than 3 mm to minimize the possibility of stump appendicitis in the future.\textsuperscript{25}

Occasionally, inflammation at the tip of the appendix makes antegrade removal of the appendix difficult. In such cases, the appendix can be removed in a retrograde fashion. In so doing, the appendix is divided at its base using one of the methods described previously. The mesoappendix is then divided between clamps, starting at the appendiceal base and progressing toward the tip (Fig. 41-8).
Retrograde dissection of the appendix. The base of the appendix is secured with a pursestring suture, transected, and dissected off the cecum.

In certain cases, the appendiceal inflammation extends to the base of the appendix or beyond to the cecum. Division of the appendix through inflamed, infected tissue leaves the potential for leakage of cecal contents with a resultant abscess or fistula. Ensuring that the resection margin is grossly free of active inflammation minimizes this risk. If the base of the cecum is also inflamed but there is sufficient noninflamed cecum between the appendix and
the ileocecal valve, an appendectomy with partial cecectomy can be performed using a stapling device.\textsuperscript{107} Care should be taken to avoid narrowing the cecum at the ileocecal valve. If the inflammation extends to the ileocecal junction, an ileocecectomy with primary anastomosis may be necessary.

After the appendix is removed, hemostasis is achieved and the RLQ and pelvis are irrigated with warm saline. The peritoneum is closed with a continuous 0 absorbable suture. This layer provides no strength but helps to contain the abdominal contents during abdominal wall closure. The internal and external oblique muscles are then closed in succession using continuous 0 absorbable suture. To decrease postoperative narcotic requirements, the external oblique fascia can be infused with local anesthetic. Interrupted absorbable sutures are typically placed in Scarpa’s fascia, and the skin can be closed with a subcuticular absorbable suture. With a preoperative dose of intravenous antibiotics and primary closure of the skin, fewer than 5% of patients with nonperforated appendicitis can be expected to develop a wound infection.\textsuperscript{108}

**Postoperative Care**

Postoperative care is similar after laparoscopic and open approaches. Patients with nonperforated appendicitis typically require a 24- to 48-hour hospital stay. Patients can be started on a clear liquid diet immediately, which can be advanced to their preoperative baseline diet as tolerated. No postoperative antibiotics are required for nonperforated appendicitis. Patients can be discharged when they tolerate a regular diet and pain is controlled on oral agents.

**PERFORATED APPENDICITIS**

When appendicitis progresses to perforation, management depends on the nature of the perforation. If the perforation is contained, a solid or semisolid periappendiceal mass of inflammatory tissue can form, referred to as a *phlegmon*. In other cases, contained perforation may result in a pus-filled abscess cavity. Finally, free perforation can occur, causing intraperitoneal dissemination of purulent fluid and fecal material. In the case of free
perforation, the patient is typically quite ill and perhaps septic. Urgent laparotomy or laparoscopy, as described above, is necessary for appendectomy and irrigation and drainage of the peritoneal cavity. Sometimes patients with free perforation present with an acute abdomen and generalized peritonitis, and the decision to operate is made without a definitive diagnosis. Depending on the clinical stability of the patient, a diagnostic laparoscopy or exploratory laparotomy through a midline incision is performed. Once perforated appendicitis is confirmed, appendectomy again proceeds as described previously. Peritoneal drains are not necessary, as they do not reduce the incidence of wound infection or abscess after appendectomy for perforated appendicitis. The final operative decision is whether or not to close the surgical site. Because of wound infection rates ranging from 30 to 50% with primary closure of grossly contaminated wounds, many advocate delayed primary or secondary closure. However, a cost-utility analysis of contaminated appendectomy wounds showed primary closure to be the most cost-effective method of wound management. Our technique of skin closure is interrupted permanent sutures or staples every 2 cm with loose wound packing in between. Removal of the packing in 48 hours often leaves an excellent cosmetic result with an acceptable incidence of wound infection. Patients continue to receive treatment with broad-spectrum antibiotics for at least 4 days after source control and should remain in the hospital until afebrile and tolerating a regular diet.

If the patient does not have signs of generalized peritonitis but an abscess or phlegmon is suspected by history and physical exam, a CT scan can be particularly helpful to confirm the diagnosis. A solid, inflammatory mass in the RLQ without evidence of a fluid-filled abscess cavity suggests a phlegmon. In such instances, appendectomy can be difficult due to dense adhesions and inflammation. Ileocececetomy may be necessary if the inflammation extends to the wall of the cecum. Complications such as inadvertent enterotomy, postoperative abscess, or enterocutaneous fistula may ensue. Because of these potential complications, many support an initially nonoperative approach. Such an approach is only advisable if the patient is not clinically ill. Nonoperative management includes intravenous antibiotics and fluids as well as bowel rest. Patients should be closely monitored in the hospital during this time. If fever, tenderness, and leukocytosis improve, diet can be slowly advanced, usually within 3 to 5 days. Patients are discharged home when clinical parameters have
normalized. Using this approach, many patients can be spared an appendectomy at the time of initial presentation.

If imaging studies demonstrate an abscess cavity, CT- or US-guided drainage can often be performed percutaneously or transrectally. Studies suggest that this approach to appendiceal abscesses results in fewer complications and shorter overall length of stay. Again, following drainage, the patient is closely monitored in the hospital and is placed on bowel rest with intravenous antibiotics and fluids. Advancement of diet and hospital discharge progress as clinically indicated.

**INTERVAL APPENDECTOMY**

Treatment following initial nonoperative management of an appendiceal phlegmon or abscess is controversial. Some recommend interval appendectomy (appendectomy performed approximately 6 weeks after inflammation has subsided), while others consider subsequent appendectomy unnecessary. Factors to be considered when advising patients on interval appendectomy include a relatively low incidence of future appendicitis (8%-10% and often associated with an appendicolith) and a morbidity associated with an interval appendectomy of approximately 11%. Importantly, malignancy was detected in 1.2% of cases, and colonoscopy is recommended after resolution of acute disease. These factors must be weighed against the higher morbidity associated with an immediate appendectomy in the setting of acute recurrent appendicitis in the future (as high as 36% when appendicitis is associated with a phlegmon or abscess) as well as the possibility of an ongoing appendiceal pathology, including inflammatory bowel disease and cancer. Because it can now be performed laparoscopically on an outpatient basis and with low morbidity, interval appendectomy should be considered for patients who were initially treated for perforated appendicitis with nonoperative management.

**NORMAL APPENDIX**

Because of the difficulty in diagnosing appendicitis, it is not uncommon for a normal appendix to be found at appendectomy. Misdiagnosis can occur more
than 15% of the time, with considerably higher percentages in infants, the elderly, and young women.\textsuperscript{40} Negative appendectomy must be avoided when possible, because of the risk of surgical complications and the cost associated with unnecessary surgery.\textsuperscript{117} Nonetheless, in certain instances, a noninflamed appendix is found at laparotomy or laparoscopy. The surgeon must then decide whether or not to remove the appendix. For multiple reasons, it is generally advisable to remove the grossly normal appendix. First, if the pain recurs and the appendix has been removed, appendicitis will no longer be a possibility and can be removed from the differential diagnosis. If the patient suffers RLQ pain in the future and the appendix has not been removed, but the patient has a classic RLQ scar, a surgeon evaluating the patient may assume a history of appendectomy and erroneously disregard appendicitis as a possible diagnosis. As LA becomes more popular, this may even become true for patients with port site scars suggestive of appendectomy. Finally, there is strong evidence that a surgeon’s gross assessment of the appendix can be inaccurate. In one study, 11 (26%) of 43 appendectomy specimens described as normal by the surgeon showed acute appendicitis on pathologic examination.\textsuperscript{118} As a result, removal of a grossly normal appendix at the time of the operation for suspected appendicitis is recommended.

When a normal appendix is discovered at appendectomy, it is important to search for other possible causes of the patient’s symptoms. The terminal ileum can be inspected for evidence of terminal ileitis, which could be from infectious causes (\textit{Yersinia} or tuberculosis) or Crohn’s disease. If Crohn’s disease is discovered and the cecum is not inflamed, appendectomy should be performed without an increase in complication rate. In the setting of cecal inflammation, appendectomy should not be performed, and appropriate medical therapy for the treatment of newly diagnosed Crohn’s disease should be initiated postoperatively. The ileum should also be evaluated for an inflamed or perforated Meckel diverticulum, which should be excised. In females, the ovaries, fallopian tubes, and uterus should be examined for pathology as well. Evaluation of the left adnexa can be difficult through an RLQ incision, highlighting the utility of laparoscopy for female patients.

**CHRONIC APPENDICITIS**

Although rare, chronic appendicitis can explain persistent abdominal pain in
some patients. Patients do not present with the typical symptoms of acute appendicitis. Instead, they endorse weeks to years of RLQ pain and may have had multiple medical evaluations in the past. When queried, they may describe an initial episode with more classic symptoms of acute appendicitis, for which no treatment was delivered. Diagnosis can be difficult, as laboratory and radiologic studies are typically normal. Because the diagnosis is often uncertain preoperatively, laparoscopy can be a useful tool to allow minimally invasive exploration of the abdomen. Pathology evaluation revealing chronic inflammation confirms the diagnosis.

ASYMPTOMATIC APPENDICOLITH

As CT imaging becomes more widely used, it is likely that an increasing number of asymptomatic appendicoliths will be discovered. As discussed previously, appendicoliths are not pathognomonic for appendicitis but should be considered in conjunction with the clinical presentation and other diagnostic studies. Lowe and colleagues compared CT imaging of children with suspected appendicitis to children with abdominal trauma. Six (14%) of 44 patients with suspected appendicitis had an appendicolith but proved not to have appendicitis. In addition, 2 (3%) of the 74 trauma patients had an appendicolith on CT. These children were not followed to see if appendicitis developed later in life, but the considerable number of asymptomatic appendicoliths seen on adult abdominal radiographs suggests that many patients with an appendicolith will never develop appendicitis. Based on this, appendectomy for asymptomatic appendicolith cannot be recommended.

NEOPLASMS OF THE APPENDIX

Neoplasms of the appendix are rare, discovered in less than 1% of appendectomies. Signs and symptoms of appendicitis prompt appendectomy in up to 50% of patients with appendiceal neoplasms, and it is not uncommon for such patients to develop acute appendicitis. Patients may also present with a palpable mass, intussusception, urologic symptoms, or an incidentally discovered mass on abdominal imaging or at laparotomy for another purpose. Typically, the diagnosis is not known until the time of operation or pathologic evaluation of the appendectomy specimen. However, preoperative
diagnosis may become more common as imaging techniques improve and become more widely used. Because of their common embryologic origin, the appendix and colon are susceptible to many of the same neoplastic growths. The most common appendiceal tumors include cystic neoplasms, neuroendocrine (carcinoid) tumors, adenocarcinoma, and metastases. Other tumors have been reported but are extremely rare, such as lymphoma, stromal tumors (leiomyoma and leiomyosarcoma), and Kaposi sarcoma.123

Cystic Neoplasms and Pseudomyxoma Peritonei

Sometimes referred to as *mucoceles*, mucinous neoplasms of the appendix include a spectrum of benign and malignant diseases, including simple cyst, mucinous cystadenoma, mucinous cystadenocarcinoma, and pseudomyxoma peritonei. Mucocele is not a true pathologic diagnosis and instead refers to the macroscopic appearance of an appendix distended with mucus. Any of the above conditions can grossly form a mucocele, but the more specific diagnostic term is more precise.124 The term low-grade appendiceal mucinous neoplasm (LAMN) can be used to refer to mucinous tumors with low-grade cytology, whereas tumors with high-grade cytology are classified as mucinous cystadenocarcinoma.125 The pathway from mucinous cystadenoma to cystadenocarcinoma is postulated to be akin to that of progression from colonic polyps to adenocarcinoma. A simple cyst results from nonneoplastic occlusion of the appendiceal lumen, is usually less than 2 cm in diameter, and is often an incidental finding at appendectomy. In contrast, mucinous cystadenomas, benign tumors that represent the majority of “mucoceles,” can grow to 8 cm or larger (Fig. 41-9).126 Patients typically remain asymptomatic due to slow-growing distension of the appendix and instead present incidentally with a mass on physical examination or abdominal imaging (Fig. 41-10). On plain radiograph or CT, wall calcification is characteristic.124 Ten-year disease-free survival progresses from 100% in low-grade mucinous neoplasms confined to the appendix, to 88% in low-grade mucinous neoplasms with extra-appendiceal acellular mucin, to 9% in low-grade mucinous neoplasms with extra-appendiceal neoplastic epithelium, to 0% in appendiceal mucinous neoplasms with poor prognostic markers of invasion, complex architecture, or high-grade cytology.127
FIGURE 41-9  A 14-cm mucinous cystadenoma of the appendix. The appendiceal tip is to the left, and the base is to the right. (Used with permission from Jacqueline M. Wilson, MD, PhD, Brigham and Women’s Hospital, Boston, MA.)
Mucinous appendiceal masses should be surgically removed because of the potential for underlying malignancy. In one study of 129 patients who underwent resection of appendiceal mucoceles, Stocchi and colleagues noted that tumor size was not statistically related to risk of malignancy. For mucinous cystadenoma, appendectomy is sufficient if the lesion does not involve the appendiceal base. Occasionally, the mass will rupture prior to or at the time of removal, but this rupture is typically contained to the RLQ and is considered localized pseudomyxoma peritonei (see below). If the mass is benign, appendectomy and removal of any residual mucin are curative. Mucinous cystadenocarcinoma represents the malignant form of cystic neoplasms of the appendix. In contrast to cystadenoma, patients are more likely to be symptomatic with abdominal pain, weight loss, an abdominal mass, or signs of acute appendicitis. Right hemicolecetomy should be performed in the setting of any indication of malignancy in an appendiceal mass with the possibility of cure. The laparoscopic approach is not generally recommended because of the possibility of malignancy and the risk of spillage of mucin-secreting cells throughout the abdomen. Because of an association with colon and rectal carcinoma, a screening colonoscopy is recommended postoperatively.

It is not uncommon, however, for the malignant diagnosis to be unknown until the pathologic evaluation of the appendectomy specimen indicates incidental appendiceal mucinous cystadenocarcinoma. In such cases, reoperation with right hemicolecetomy is recommended, as 5-year survival for mucinous cystadenocarcinoma is 75% after hemicolecetomy and less than 50% after appendectomy alone. Some referral centers advocate extensive initial resections including omentectomy, as well as repeated debulking procedures for recurrent disease.

Pseudomyxoma peritonei is a condition in which tumor perforation has seeded the peritoneum with mucinous tumor cells. On physical exam, increasing abdominal girth may also be present, suggesting perforation and peritoneal dissemination of mucin-secreting cells characteristic of
pseudomyxoma peritonei. Diffuse pseudomyxoma peritonei is highly predictive of malignancy; in one series, 95% of patients with pseudomyxoma had an associated mucinous cystadenocarcinoma. The recommended treatment consists of a minimum of a right hemicolecctomy with debulking of any gross spread of disease and removal of all mucin. Recently, hyperthermic intraoperative chemotherapy (HIPEC) is increasingly being used. Chua and colleagues report results from a large multicenter study of 2298 patients with pseudomyxoma peritonei from appendiceal origin who were treated with cytoreductive surgery and HIPEC. The authors document a median survival and progression-free survival of greater than 16 and 8 years, respectively. Outcomes were significantly worse for those with gross residual disease after debulking surgery. Data from a French multicenter study indicate that patients with pseudomyxoma peritonei should be referred to centers with experience in their treatment, as higher center volume was significantly associated with improved disease-free survival. Long-term management involves debulking for symptomatic disease, with a high likelihood of repeated surgery.

**Adenocarcinoma**

Primary adenocarcinoma of the appendix is classified into 3 types: mucinous (discussed previously), colonic, and signet-ring cell. The colonic type is least common, least likely to secrete mucin, and most likely to present with acute appendicitis due to obstruction of the appendiceal lumen. Staging is distinguished from that of colonic adenocarcinoma in the American Joint Committee on Cancer staging manual. The colonic type has a less favorable prognosis, with only 41% 5-year survival after treatment, compared to 71% for the mucinous type. The optimal treatment is right hemicolecctomy, and reoperation should be recommended if the diagnosis is made on pathologic evaluation of an appendectomy specimen. Signet-ring cell type confers the poorest prognosis. The effectiveness of adjuvant chemotherapy or radiotherapy on primary appendiceal adenocarcinoma is unknown. HIPEC may be considered for patients with disseminated appendiceal adenocarcinoma, with promising results from a series of 46 consecutive patients with median overall survival and disease-free survival of 56.4 months and 20.5 months, respectively.
Carcinoid Tumors

The most common neoplasm of the appendix, carcinoid tumors, compose more than 50% of all appendiceal tumors. Among malignant tumors of the appendix, carcinoids are less aggressive and carry a much more favorable prognosis than adenocarcinomas, with 5-year survival approaching 90%. Most appendiceal carcinoids are found incidentally at the time of appendectomy for appendicitis. However, perhaps because the majority of appendiceal carcinoids are located at the tip of the appendix, the carcinoid mass is the cause of appendicitis only 25% of the time. Tumor size, extent of disease, and histology are the primary determinants of malignant potential. Approximately 75% of carcinoids are less than 1 cm in size and only 5% to 10% are over 2 cm. Lymph node invasion and distant metastases are rare except in tumors over 2 cm. In a pooled summary of 517 patients, nodal metastasis were found in 0%, 7.5%, and 33% of patients with tumors ≤1 cm, 1.1 to 1.9 cm, and ≥2 cm, respectively.

Goblet cell carcinomas were previously categorized as a subtype of carcinoid but have characteristics of both carcinoid and adenocarcinoma. Goblet carcinoma behaves more aggressively than classic carcinoid but still has a better prognosis than adenocarcinoma. Reflecting this in a study of 2812 patients with appendiceal neuroendocrine tumors in the National Cancer Database, Hsu and colleagues reported a 5-year overall survival rate of 86% for malignant carcinoid tumor, 78% for goblet cell carcinoid, and 56% for composite goblet cell carcinoid-adenocarcinoma.

Treatment of appendiceal carcinoid is dictated primarily by tumor size. Regardless of the operation, it is important to visually inspect and palpate the bowel to investigate the possibility of multifocal disease. Simple appendectomy is sufficient for tumors less than 1 cm in diameter because of the low likelihood of lymph node involvement. Among patients with tumors of 1 to 2 cm in diameter, right hemicolecotomy is reserved for patients with positive margins or deep mesoappendiceal invasion, higher proliferation rate (grade 2), or angioinvasion. For masses larger than 2 cm, right hemicolecotomy is recommended. Because of a concern for increased metastatic potential, some authors also advocate right hemicolecotomy regardless of tumor size in the setting of young patients; carcinoids at the appendiceal base; and/or histopathologic evidence of lymphatic invasion,
lymph node involvement, spread to the mesoappendix, tumor-positive resection margins, or cellular pleomorphism with a high mitotic index.\textsuperscript{139}

**SMALL BOWEL DIVERTICULA**

Small bowel diverticula can be characterized according to their anatomic location (duodenal, jejunoileal, and distal ileal diverticula) or the type of diverticula (false or true diverticula). Small bowel diverticula are typically false diverticula, which by definition do not contain all the layers of the bowel wall and involve herniated mucosa and submucosa. They occur at points of weakness, where blood vessels enter the mesenteric border of the small bowel. In contradistinction, intraluminal diverticula occur from congenital abnormalities. Finally, a distal ileal (Meckel) diverticulum is a true diverticulum containing all of the layers of the small bowel. It is a congenital anomaly resulting from the failure of the vitelline duct to obliterate and is located along the antimesenteric border of the distal ileum. Although the presence of small bowel diverticula is not uncommon, most are asymptomatic and thus never appreciated. Fewer than 4\% of small bowel diverticula cause symptoms, including inflammation, hemorrhage, obstruction, perforation, and malabsorption.

**Duodenal Diverticula**

Duodenal diverticula (DD) account for approximately 45\% of small bowel diverticula and have a reported incidence on radiologic and autopsy studies of 5\% to 22\%.\textsuperscript{140} They are rarely multiple (12\%), and the vast majority (88\%) are located in the medial wall of the second portion of the duodenum.\textsuperscript{141} When the diverticulum is located adjacent to the ampulla of Vater, as is often the case, it is known as a perivaterian or periampullary diverticulum. DD typically occur in patients age 50 to 65 years and are often asymptomatic at presentation. Less than 5\% of patients with DD present with symptoms, including nausea, vomiting, RUQ abdominal pain, fevers, chills, and bleeding. These presentations are often noted in case reports and result from one of many potential complications, including inflammation, obstruction of the duodenum or biliary-pancreatic duct, fistula formation in the bile duct, bezoar formation inside the diverticulum, and perforation. Although it is the
most unusual complication, DD perforation is the most serious and can carry a mortality of up to 20%. Perforation usually results from acute inflammation but may also result from enterolithiasis, ulceration, increased intraluminal pressure (e.g., during endoscopy), abdominal trauma, gallstones, or ischemia. Perforation usually occurs posteriorly and thus can result in a retroperitoneal abscess and sepsis. Anterior perforation can also occur, resulting in intraperitoneal spillage or communication with surrounding structures. Of resultant fistulae, including to the pancreas, colon, and gallbladder, the most catastrophic is duodenal perforation into the aorta.

The nonspecific nature of the presenting symptoms and their commonality with other gastrointestinal diseases such as pancreatitis, cholecystitis, cholangitis, and peptic ulcer disease highlight the fact that the diagnosis of a complicated DD is often one of exclusion (unless one of the aforementioned unique presentations occurs). Radiologic studies including plain abdominal films and US may be helpful to exclude other etiologies but are not definitive. CT imaging and upper endoscopy are the modalities of choice for evaluation. In the case of an inflamed diverticulum, CT may demonstrate a thickened duodenal wall and surrounding fat inflammation. If perforation has occurred, an extraluminal collection of air and fluid (predominantly retroperitoneal) may be identified. In addition, the administration of oral contrast with a CT scan or an upper gastrointestinal swallow study may define the extent of a leak in the case of a perforation. However, it is rare to identify a DD on CT scan, and additional studies may be required. Side-viewing endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) are valuable in correctly diagnosing the presence of a DD as well as potentially treating some of the associated complications. Successful endoscopic management of hemorrhage, duodenal obstruction, pancreatobiliary obstruction resulting in pancreatitis or cholangitis, and retroperitoneal abscess drainage associated with a DD have been reported.\textsuperscript{142}

The management of DD depends on the presence or absence of symptoms and the clinical stability of the patient. Given the precarious typical location of a DD near the ampulla of Vater and the concomitant morbidity associated with resection, asymptomatic DD discovered on imaging or endoscopy for other reasons should be observed. Symptomatic DD can be managed endoscopically, nonoperatively, or with surgical exploration and resection or bypass. If inflammation with or without perforation is present, nonoperative management, including nasogastric decompression, antibiotics, serial
examinations, and radiologic-guided drainage if an abscess is present, has been reported. This approach can be considered in patients with mild symptoms who are clinically stable or when CT confirms a contained leak.\textsuperscript{140-142} If the patient is not a candidate for nonoperative management because of hemodynamic instability, generalized peritonitis, or persistent severe symptoms, the choice of surgical intervention depends on such factors as the location of the diverticulum and other intraoperative findings. In the setting of minimal inflammation and favorable diverticular anatomy, a simple closure of the perforated diverticulum or diverticulectomy with single- or double-layer duodenal closure after Kocherization of the duodenum is the treatment of choice. After repair, appropriate drainage tubes should be placed and the greater omentum can be used to reinforce the repair. It is imperative to avoid damaging the pancreatic and distal common bile ducts during the repair, so cannulation of the ampulla of Vater (either retrograde or antegrade through the cystic duct with subsequent cholecystectomy) can be performed to help visualize the ampulla prior to dissecting the diverticulum. At times, diverticular anatomy is unfavorable with significant inflammation at the site of the diverticulum, the diverticulum buried in the pancreatic head, or the papilla located deep in the diverticulum. In such cases, a diversion should be performed by either a distal gastrectomy with a Billroth II reconstruction or a Roux-en-Y gastrojejunostomy. Again, appropriate drainage tubes are typically placed to decompress the affected areas. In addition to diversion and diverticulectomy, segmental duodenal resection for a perforated DD has also been reported for the rare case of a DD located in segment III or IV of the duodenum. A pancreaticoduodenectomy may also be necessary if the DD lies in close proximity to the common bile and pancreatic ducts and the inflammation is thought to be too severe for safe diversion or drainage.\textsuperscript{140,142} If symptoms derive from obstruction of the pancreaticobiliary system, causing cholangitis or pancreatitis, resection of the duodenum may not be required. In such cases, treatment may consist of diversion of bile flow with a Roux-en-Y choledochojejunostomy and duodenojejnuostomy.\textsuperscript{142}

\textbf{Jejunoileal Diverticula}

The least common of the small bowel diverticula, jejunoileal diverticula (JID) have a rare prevalence of 0.002% to 5% based on postmortem and enteroclysis studies. The risk of diagnosis increases with age and peaks in the
sixth and seventh decades of life. JID are acquired pseudodiverticula believed to result from a jejunoileal dyskinesia causing increased intraluminal pressures and ultimately herniation of the mucosa and submucosa through the weakest site of the muscularis propria of the bowel wall (ie, the mesenteric border where paired blood vessels enter the bowel wall). They can be single (33%) or multiple (66%) and located in the jejunum (55%-80%), ileum (15%-38%), or both (5%-7%). Interestingly, patients with JID also frequently have other coexisting gastrointestinal diverticula, including those found in the colon (20%-70%), duodenum (10%-40%), esophagus, and stomach (2%), highlighting a potential common etiology.

Most patients with JID are asymptomatic (up to 70%). When symptomatic, the diagnosis of a JID is often challenging because patients often present with vague abdominal symptoms. There is no gold standard imaging technique used to diagnose a JID. Upper gastrointestinal studies with small bowel follow-through as well as traditional enteroclysis and CT enteroclysis studies are beneficial. CT, tagged red blood cell scan, or angiogram may demonstrate findings consistent with a complication of a JID such as inflammation, perforation, or bleeding. Capsule endoscopy and double-balloon endoscopy are useful in diagnosing small bowel disorders and may be of benefit in identifying JID in a nonacute setting. Ultimately, JID are often identified on exploratory laparotomy or laparoscopy for other indications or for the evaluation of chronic or acute symptoms.

Asymptomatic, incidentally discovered JID need not be resected. When symptomatic, patients with JID can be divided into those with acute or chronic symptoms. Forty to 60% of patients with a known diagnosis of JID present with chronic symptoms. These symptoms are often nonspecific and include nausea, vomiting, postprandial bloating, recurrent abdominal pain, cramping, weight loss, fatigue, and failure to thrive. Because of the vague nature of the presenting symptoms, these patients often go undiagnosed or misdiagnosed for several months (average 22 months) prior to being correctly diagnosed. The underlying pathophysiology of the chronic symptoms is believed to be related to either intestinal dyskinesia or bacterial overgrowth from blind loop syndrome due to stasis in the diverticular lumen. When bacterial overgrowth and a blind loop syndrome are present, the patient may develop malabsorption, steatorrhea, and megaloblastic anemia resulting from vitamin B\textsubscript{12} deficiency. Frequently, chronic symptoms from JID can be
successfully managed medically. Medical management consists of a low-residue diet, antispasmodics, antacids, analgesics, and vitamin B\textsubscript{12} supplementation. Bacterial overgrowth and blind loop syndrome can be initially managed with antibiotics. In the rare case in which medical management fails, patients may require resection of the segment of bowel containing the diverticulum with subsequent primary anastomosis.

Approximately 10% to 19% of patients with JID present with acute, often emergent, symptoms resulting from a complication of the diverticulum, including gastrointestinal hemorrhage, diverticulitis, obstruction, fistula formation, and perforation. The presentation and management of a patient with an acute complication of a JID depend on the complication. Inflammation resulting in diverticulitis occurs in 2.3% to 6.4% of patients with JID and can present as mild abdominal pain or diffuse peritonitis associated with free perforation.\textsuperscript{143} If perforation occurs in the setting of full-thickness necrosis, it can be associated with a mortality of up to 40%.\textsuperscript{143} Traumatic and foreign body perforations of JID have also been described. If the perforation is contained within the mesentery, nonoperative management with bowel rest and antibiotics with or without percutaneous drainage can be attempted. Similarly, in a clinically well patient, asymptomatic pneumoperitoneum in the setting of a known JID is not an absolute indication for surgery and this scenario may be managed nonoperatively.\textsuperscript{143} Lack of clinical improvement after a period of nonoperative management, however, mandates resection of the affected segment of bowel with a primary anastomosis. Similarly, patients presenting with more significant findings of fever, elevated WBC, peritonitis, and septic physiology require immediate laparotomy with resection of the affected segment of bowel.\textsuperscript{143}

Of patients with JID, 2% to 4.6% present with obstruction related to adhesions, intussusception, volvulus, and extrinsic compression from a fluid-filled diverticulum or, rarely, from an enterolith formed in the diverticulum causing obstruction at the diverticulum or at the ileocecal valve. Obstruction believed to be secondary to adhesions can initially be managed conservatively. However, if nonoperative management fails, lysis of adhesions and segmental bowel resection of the JID with a primary anastomosis are required. Similarly, surgical resection is indicated for the management of obstruction resulting from intussusception, volvulus, or extrinsic compression.\textsuperscript{144} Enterolith ileus associated with a JID is best
managed by an initial attempt at manual lysis of the stone without an enterotomy. If not possible, the stone can be retrieved, advanced into the colon, and/or mechanically fractured through an enterotomy performed in a nonedematous segment of bowel. If 1 or multiple diverticula appear inflamed or scarred, segmental resection of the involved bowel with a primary anastomosis is mandated. However, many patients often have multiple diverticula over a long stretch of bowel, and thus, if no evidence of inflammation or scarring is present, avoiding resection is indicated. Approximately 3% to 8% of patients with JID present with bleeding complications. Hemorrhage from a JID can be slow and chronic in nature or acute and massive presenting with hemorrhagic shock. Upper and lower endoscopies are often negative, and the diagnosis is made with angiographic and radioactive red blood cell studies. Although successful intervention with angiographic embolization has been documented, segmental bowel resection is frequently the required treatment.

**Meckel Diverticula**

Meckel diverticula are the most common congenital malformations of the gastrointestinal tract, occurring in 1% to 3% of the population. A Meckel diverticulum is a true diverticulum containing all 3 layers of the intestinal wall. The structure results from the failure of the obliteration of the vitelline (omphalomesenteric) duct, which normally occurs during the fifth to seventh weeks of fetal life. Blood supply derives from the vitelline artery, a branch of the superior mesenteric artery. It is typically located on the antimesenteric border of the small bowel within 100 cm of the ileocecal valve. Although Meckel diverticula are often lined with ileal mucosa, they may also contain ectopic gastric, duodenal, colonic, and endometrial mucosa as well as pancreatic tissue, carcinoid tissue, Brunner’s glands, and hepatobiliary tissue. Gastric mucosa, followed by pancreatic tissue, is the most commonly occurring heterotopic tissue.

Similar to other small bowel diverticula, the majority of Meckel diverticula are asymptomatic and discovered incidentally at the time of an operation for other indications. Recent reviews indicate that up to 84% of Meckel diverticula found at operation were asymptomatic. A symptomatic Meckel diverticulum can present in both the pediatric and adult population.
However, the frequency of presentation decreases with increasing age. There is a male predominance (3:1) of both symptomatic and asymptomatic Meckel diverticula in both pediatric and adult populations.\textsuperscript{147}

Symptomatic presentation results from one of many potential complications, including bleeding, obstruction, diverticulitis, perforation, intussusception, ulceration, and, rarely, the presence of malignancy within the Meckel diverticulum. In the adult population, the most common presentations are bleeding (38%), obstruction (34%), and diverticulitis (28%). In the pediatric population the most common presentations are obstruction (40%), bleeding (31%), and diverticulitis (29%).\textsuperscript{147,148} Obstruction may result from the Meckel diverticulum serving as a lead point for intussusception, a point of fixation for volvulus, or as a result of an adhesive band to the diverticulum. Bleeding in the setting of a Meckel diverticulum is believed to result from acid secretion from ectopic gastric mucosa, leading to ulceration of and subsequent bleeding from ileal mucosa. The typical presentation is episodic, painless gastrointestinal hemorrhage. The most common sites of ulceration are the base of the diverticulum at the juncture between ectopic gastric and ileal mucosa, followed by the mesenteric ileal mucosa. Among patients who develop malignancy in the Meckel diverticulum, carcinoid predominates. Finally, just as an Amyand hernia contains the appendix, a Littre hernia contains a Meckel diverticulum. The most common type of Littre hernia is inguinal in adults and umbilical in children.\textsuperscript{149}

Preoperative diagnosis of a symptomatic Meckel diverticulum can be difficult. A technetium-99m pertechnetate scan is the most accurate noninvasive study used to interrogate the presence of a Meckel diverticulum. The tracer used in this study is specific for ectopic gastric mucosa, and thus false-positive results may occur when a duplication cyst containing gastric mucosa is present. A false-negative result occurs if the Meckel diverticulum does not contain ectopic gastric mucosa. During the study, a bladder catheter can be used to avoid accumulation of contrast media obscuring the area of interest. Despite these limitations, studies have found technetium-99m pertechnetate scans to be highly sensitive and specific in both the pediatric and adult populations.\textsuperscript{147} In cases of a suspected bleeding Meckel diverticulum, angiography, and a tagged red blood cell scan may be of diagnostic value. If suspicion is high, other etiologies have been ruled out, and noninvasive diagnostic tools exhausted, exploratory laparoscopy may be used to diagnose and treat a complicated Meckel diverticulum.
Surgical resection is indicated for symptomatic Meckel diverticula. Options for resection include a diverticulectomy or a segmental bowel resection with a primary anastomosis. Indications for segmental bowel resection include damage to the normal ileal mucosa due to ulceration or bleeding as well as the presence of diverticulitis or palpable ectopic tissue at the diverticular-intestinal junction. In other circumstances, a diverticulectomy can be performed if amputating the diverticulum at its base will not compromise the ileal lumen. If diverticulitis is present, the line of resection should be free of inflammation. Amputation should be performed in a transverse orientation and can use a surgical stapling device. The staple line can then be oversewn with interrupted 3-0 silk Lembert sutures. Alternatively, the diverticulum can be resected between bowel clamps and the defect sutured closed transversely in 2 layers, using a continuous inner layer of 3-0 Vicryl or chromic suture followed by an outer layer of 3-0 silk Lembert sutures. In either case, the surgeon should identify and ligate the artery perfusing the Meckel diverticulum.

For an asymptomatic Meckel diverticulum incidentally discovered on imaging study, we recommend nonoperative management. The potential benefit of an operation is outweighed by the high number needed to treat (n = 758) and the risk of complications with diverticulectomy or bowel resection. For an asymptomatic Meckel diverticulum incidentally discovered during an operation, the appropriate action is slightly less clear and likely depends on patient selection. In a meta-analysis that includes nearly 3000 patients, Zani and colleagues report that the postoperative complication rate was significantly higher among patients who underwent incidental diverticulectomy (5.3%) compared to those with the Meckel diverticulum left in situ (1.3%). Furthermore, of the 64 patients included in the systematic review who did not undergo resection of their asymptomatic Meckel diverticulum, none developed complications with long-term follow-up. Caution should be used when interpreting these data, which incorporate the findings of dated and retrospective studies. The authors proceed to argue that appendicitis is 50-fold more likely to occur than symptomaticity from a Meckel diverticulum. While incidental appendectomy has become an obsolete practice, incidental diverticulectomy may have even less utility.

Despite this, the risk of developing symptoms was estimated to be as high as 6%, and selected asymptomatic patients may be at higher risk than others.
As such, some authors support incidental diverticulectomy for any patient who fulfills any of the following criteria: (1) younger than 50 years, (2) male sex, (3) diverticulum greater than 2 cm in length, and (4) ectopic or abnormal features within a diverticulum. These criteria are based on a review of 1476 patients who underwent incidental diverticulectomy at a single institution between 1950 and 2002. Of those, 1238 patients were asymptomatic and 238 were symptomatic. The aforementioned criteria were significantly associated with symptomaticity in multivariable analysis. The decision to resect an asymptomatic Meckel diverticulum should be made on a case-by-case basis, based on these patient factors.

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INTRODUCTION

Intestinal failure (IF), including surgical short bowel syndrome (SBS), is a life-threatening condition that is associated with several major medical complications as well as limitations in quality of life. The evolution of treatment strategies for IF/SBS has seen significant changes in the past 30 years. Like several major advances in surgery, the discovery of anastomotic techniques by Alexis Carrel in the early 1900s paved the way for intestinal transplantation (ITx). As a parallel to surgical discoveries, the development and implementation of parenteral nutrition (PN) and hormonal analogs has allowed clinicians to support IF patients and bridge them toward the ultimate therapy of ITx. The purpose of this chapter is to provide an overview of the causes and medical management of IF/SBS, indications for and various
surgical techniques within ITx. The chapter reviews the landmark developments in surgical therapy techniques and provides an outline for the different technical variations within ITx.

BACKGROUND/HISTORY

The evolution in the medical management of IF/SBS has relied heavily on the advent of PN. Prior to 1968, patients who suffered a massive infarction of their small intestine were often left unresected at the time of laparotomy due to the lack of intravenous nutritional support in the perioperative setting. This often led to consecutive operations for resections of necrotic bowel and patients would ultimately succumb to sepsis and multiorgan failure. The first major breakthrough for PN was ushered in as an alternative therapy for the IF patient in 1968. Wilmore and colleagues were able to demonstrate that the infusion of a hypertonic nutrient solution through a dedicated central venous catheter (CVC) could deliver all of the necessary nutrients to sustain growth and development in an infant with intestinal atresia and IF/SBS. This development was a major stepping stone that paved the way for the surgical developments that followed.

Richard Lillehei and Thomas Starzl established the early techniques of ITx in canine models in the 1950-1960s. However, the first reports of ITx came in the mid-1980s when Williams, Starzl, and others documented the first successful isolated intestine, multivisceral, and liver-intestine transplants in humans. Together, these landmark medical and surgical establishments set the groundwork for the modern era of ITx.

PATHOPHYSIOLOGY OF INTESTINAL FAILURE AND ADAPTATION

The complex mechanisms and relationships of the neurohormonal, enteric nervous, and immune systems of the intestine are beyond the scope of this chapter. However, it must be noted that IF/SGS results from an inadequate delivery of micronutrients, fluid, and electrolytes via the gastrointestinal tract. In the IF/SBS patient, compensatory mechanisms of adaptation can be achieved in the remnant bowel in an attempt to restore the threshold for
Clinically, the cornerstone of successful adaptation relies upon enterocyte mass. Likewise, patients with a greater length of functional bowel and the presence of an ileocecal valve (ICV) are likely to succeed at achieving an adapted state. The functional response of the remnant gut in the IF/SBS patient is primarily to modify sodium, water, and glucose absorption. Enterocyte hyperplasia contributes to increasing enterocyte mass; however, modifications in enterocyte-specific gene expression that leads to improved nutrient trafficking also adds a functional increase to the enterocyte mass, thus rendering an adapted state. These molecular mechanisms have been the foundation that have led to the surgical concepts which focus on bowel lengthening procedures. The techniques such as the Bianchi and the serial transverse enteroplasty (STEP) procedures strive to increase overall enterocyte mass, and these are discussed in further detail later in this chapter.

### INTESTINAL FAILURE: DEFINITIONS AND CLASSIFICATIONS

Historically, “short bowel syndrome” was a blanket term that had been used for patients who suffered a catastrophic loss of bowel length that rendered them incapable of maintaining enteral nutrition. These patients were all managed with total parenteral nutrition (TPN), and thus there was no need to further stratify the definition or causes of IF. Advances in prenatal and neonatal intensive care along with more recent developments in medical therapies such as recombinant growth hormone, somatostatin, and glucagon-like peptide-2 (GLP-2) analogs have forced us to further classify the definition of IF. In 2006, a group of experts developed a consensus definition whereby “Intestinal failure results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance.” With a well classified definition, we are now better able to evaluate the relative efficacy of these therapies and thus offer some patients the opportunity to regain nutritional autonomy free of PN or intravenous fluids. Thus, it is important to recognize that while IF can occur as a result of surgical resection of the gut (“short bowel syndrome”) it can also result from conditions that disrupt gastrointestinal motility or enterocyte function. In these latter cases, the length of remnant intestine is irrelevant and
usually normal.

**PEDIATRIC CAUSES OF INTESTINAL FAILURE**

The pathogenesis of IF in the pediatric population can be classified into (1) anatomic/surgical reductions of bowel (necrotizing enterocolitis, intestinal atresia, gastroschisis, and midgut volvulus), (2) neuromuscular diseases of the gut (intestinal aganglionosis or Hirschsprung disease), chronic intestinal pseudoobstruction, and (3) congenital diseases of the intestinal epithelium (microvillous atrophy, tufting enteropathy, intestinal epithelial dysplasia). In some cases, overlap can occur as in a pseudo-obstruction patient with multiple small bowel resections. The details of the complex medical management and maintenance of nutrition in this patient population is beyond the scope of this chapter. However, it must be noted that growth can be achieved on long-term PN, and the aim of appropriate medical management should be to prevent complications of PN such as catheter-related sepsis and vascular thrombosis. Moreover, a combined use of early enteral feeding with supplemental PN can help prevent intestinal failure–associated liver disease (IFALD) as the ultimate complication of PN use.

**ADULT CAUSES OF INTESTINAL FAILURE**

IF within the adult population is largely attributable to massive resection of bowel following a catastrophic event suffered by the patient. Generally, it is the result of a surgical complication from a previous procedure. However, adult causes of IF can be categorized into iatrogenic complications, ischemic complications, infiltrative disease processes, obstruction related, and functional problems (see Table 42-1).

**TABLE 42.1: ETIOLOGIES OF INTESTINAL FAILURE**
When referring to iatrogenic complications, we will focus on how IF/SBS can occur as a result of bariatric surgery for example. These patients are at risk of developing postoperative adhesions, incisional hernias, mesenteric ischemia, and internal hernias that can occur after a mesenteric defect is created during Roux-en-Y gastric bypass (RYGB) surgery. Internal hernias can develop through this defect that result in an obstruction and ultimately infarction of significant segments of bowel. The incidence of internal hernias is approximately 5% in patients who have undergone RYGB. The three main locations where internal hernias can develop are posterior to the roux limb mesentery known as the Petersen hernia, through the mesenteric defect created for the jejunojejunostomy, or through the transverse mesocolic defect created for a retrocolic roux limb (Fig. 42-1). Although the incidence of internal hernias is low, the treatment of this complication is highly time-sensitive and if left unexplored, catastrophic loss of bowel can occur that renders the patient with SBS if they are even able to survive the initial insult.

<table>
<thead>
<tr>
<th>Iatrogenic</th>
<th>Ischemic</th>
<th>Infiltrative</th>
<th>Obstructive</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt trauma</td>
<td>Arterial embolism</td>
<td>Desmoid tumors</td>
<td>Adhesive</td>
<td>Pseudoobstruction</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>Venous occlusion</td>
<td>Carcinoid</td>
<td>Internal hernia</td>
<td>IBD</td>
</tr>
<tr>
<td>Operative misadventure</td>
<td>Low flow/shock</td>
<td>Amyloidosis</td>
<td>Radiation enteritis</td>
<td>Bacterial overgrowth</td>
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<td>Malignancy</td>
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Ischemic events can be classified based on the distribution of blood supply to the bowel; namely, the celiac axis, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA). The celiac trunk supplies blood to the liver, stomach, duodenum, and the foregut up to the proximal jejunum. The SMA takes over and perfuses the remainder of the small bowel and the colon up to the splenic flexure. Finally, the IMA supplies blood to the remainder of the colon and rectum. Ischemia to these segments of bowel can occur as a result of direct trauma from penetrating missile/stab injuries or blunt trauma, as described by Asensio in his multi-institutional, retrospective series. In this review, the authors highlighted that although the incidence of these injuries is minimal, at approximately 1%, they are often lethal and the patients who survive are often left with a short segment of bowel. More commonly, embolic events from atrial fibrillation and severe atherosclerotic vascular disease results in perfusion defects, with the most devastating being to the SMA. These patients can often present with the sine qua non of “pain out of proportion to physical exam”; however, the onset of symptoms can be insidious, and late intervention is often fatal. After diagnosis with helical CT
scan, angiographic or open embolectomy is often undertaken with the hopes of instituting thrombolytic therapy and reconstituting blood flow. The advantage of open procedures in this scenario is the ability to inspect the bowel and thus facilitate a second-look laparotomy if needed.

Mesenteric venous thrombosis is another type of vascular insult that can occur, although less commonly. The most common clinical scenario is that of a chronically ill or institutionalized patient who becomes progressively dehydrated, resulting in venous thrombosis. Without sufficient outflow, the bowel becomes progressively engorged, ultimately restricting arterial inflow resulting in ischemia. In previously healthy individuals, mesenteric venous thrombosis can often occur after routine laparoscopic surgery as a result of pressure effects from pneumoperitoneum. These clinical scenarios often coincide with an underlying hypercoagulable disorder such as Protein S or C deficiency that contributes to the mesenteric venous thrombosis.\(^\text{18}\)

The infiltrative processes that lead to IF/SBS are from small bowel amyloidosis or desmoid, carcinoid, and other metastatic tumors that not only invade the bowel wall but can often infiltrate the vasculature at the mesenteric root, compromising long segments of bowel. Desmoid tumors are often associated with Gardner syndrome, and these tumors create a desmoplastic reaction with a subsequent area of dense fibrosis that cause local obstructions and enterocutaneous fistulae formation.\(^\text{19}\) Carcinoid tumors (see Chapter 40) are similar to desmoids; however, they are also notorious for mesenteric involvement, with a dense desmoplastic reaction that results in much wider areas of bowel resection.\(^\text{19}\) Finally, metastatic cancers that infiltrate the small bowel or retroperitoneum such as gynecologic tumors, colon cancers, and retroperitoneal sarcomas can all cause the same degree of local destruction as primary bowel tumors.

Functional causes of IF/SBS are largely due to pseudo-obstruction, Hirschsprung disease, or scleroderma, which were briefly mentioned in the “Pediatric Causes of Intestinal Failure” section. These are pure motility disorders that affect the transit and ultimate absorption of nutrients. The functional causes of IF/SBS are generally diagnosed at a young age, although they can progress into adolescence and even early adult years if patients can be maintained on effective PN.

Crohn’s disease is mainly classified as a mucosal etiology of IF/SBS (see Chapter 46). Although SBS is classically defined by having less than 200 cm
of bowel, Crohn’s results in SBS due to the malabsorption that occurs at the mucosal surface, rendering patients with normal bowel length functionally with SBS. The severe forms of Crohn’s disease result in IF/SBS through the development of fistulae, bowel perforations, and abscesses which frequently necessitate surgical resection and subsequent gradual shortening of bowel.\textsuperscript{20} The cornerstone of treatment for Crohn’s disease are the aminosalicylates, antibiotics, corticosteroids, and immunosuppressants such as Azathioprine and 6-mercaptopurine. However, newer therapies such as anti-TNF drugs (infliximab, adalimumab) are being used with the intention to reduce morbidity and the amount of bowel resections that are associated with moderate to severe Crohn’s disease.\textsuperscript{21} In an effort to ward off the need for ITx, bowel lengthening procedures such as the STEP procedure and stricturoplasty are often being employed in order to preserve bowel length in Crohn’s patients.\textsuperscript{22,23}

Intractable diarrhea of infancy comprises a spectrum of disorders that includes microvillous atrophy or microvillous inclusion disease, tufting enteropathy, and autoimmune enteropathy. The general features of these congenital enteropathies are that they affect the development of the intestinal mucosa that leads to intractable diarrhea during infancy and is not related to a bacterial or viral pathogen. The clinical features of these disorders are large volume diarrhea associated with electrolyte abnormalities and the ultimate need for PN. Although the clinical features are distinct, diagnosis is most commonly achieved with histopathological analysis.

**ASSESSMENT OF SBS-ASSOCIATED INTESTINAL FAILURE**

Patients with SBS and IF/SBS often have very complex past medical histories and the approach to their care can be overwhelming. When evaluating these patients, it is of paramount importance to approach the evaluation in a consistent, systems-based manner. Langnas et al. best described the components of the history and physical evaluation as follows:

1. A thorough review and summary of the past medical record. This is extremely important and painstaking. Every effort should be made to review appropriate surgical and pathological documentation to confirm
the preexisting diagnoses.

2. The cause of SBS, the anatomy and length of the intestine, including a detailed review of prior surgical procedures and any related complications. Upper GI small bowel series, barium enema, and endoscopic studies should be reviewed to determine the anatomy of the remnant bowel and anastomotic locations.

3. The number of central lines and the reasons they were changed.

4. Causal microorganisms for central line infections.

5. Nutritional assessment including parenteral and enteral intake, daily caloric requirements, and macro- and micronutrient components of PN.

6. Laboratory evaluation including serum electrolytes, liver function tests, glomerular filtration rate (GFR), albumin/prealbumin, prothrombin time, vitamin B$_{12}$, fat-soluble vitamins, serum citrulline, and stool calprotectin levels.

7. Detailed vaccination status.

8. Complete physical exam with focus on hydration status, nutritional status (height, weight, basal metabolic index), type of central line, and inspection for signs of nutritional deficiencies and complications from PN such as dermatitis or signs of chronic liver disease.$^{24}$

**PARENTERAL NUTRITION IN THE INTESTINAL FAILURE PATIENT**

Prognostic factors for adaptation include length of remnant bowel, location (ileum>jejunum), presence of ICV, absence of stoma, presence of colon in continuity, absence of liver disease, age of patient, time since onset, and the absence of an underlying GI disease/disorder. Of the aforementioned factors, the length and function of a patient’s remnant bowel are the main parameters that determine the need for PN dependence. In all cases of IF/SBS, it is critical to first assess the ability to maintain at least partial enteral nutrition, as it has been shown that partial feeding via the enteral route is associated with a better prognosis than a nonfunctioning gut.$^{25}$ Thus, exclusive use of PN should be avoided because this population of patients has the highest incidence of vascular, infectious, and metabolic complications including IFALD.$^{26-30}$ To that end, a thorough assessment to determine the ability to
establish intestinal/colonic continuity and to surgically correct any forms of obstruction in order to restore intestinal continuity should be carried out prior to initiating PN.

The typical PN formula contains macronutrients (in the form of hypertonic dextrose up to 70%), lipids, amino acids, vitamins, minerals, electrolytes, and fluid. Conceptually, the dextrose is included as a source of carbohydrate delivery, protein as crystalline amino acids, lipids provide essential fatty acids, and sterile water helps meet the patient’s fluid requirements. It should also be noted that all of the components of PN including electrolytes, vitamins, and trace elements play a collaborative role in nutritional efficiency, and along with energy, in maintaining a positive nitrogen balance. Thus, when instituting a home PN plan, it is important to ensure that the patient and caregivers are properly trained and capable of executing the plan at home.

**COMPLICATIONS OF PARENTERAL NUTRITION**

Problems related to PN can be broken down into three categories: catheter-related, metabolic, and organ dysfunction. Catheter-related problems are the most demanding components of caring for IF/SBS patients; however, it must be recognized that these catheters and maintenance of vascular access are literally the lifelines for these patients. Ideally, CVCs should be tunneled and placed in the superior vena cava (SVC) with the tip outside of the heart borderline on the post-procedure chest x-ray. These catheters should ideally be reserved for PN only and should be single lumen, although patients who are chronically requiring other intravenous solutions such as IV antibiotics or frequent replacement fluids may benefit from a dual-lumen catheter.

CVC thrombosis and occlusion are the most common complications associated with the use of these catheters, having been reported in up to 60% of patients. However, CVC-related infections carry a very high morbidity and if not recognized early can be fatal. The single most common organism that is being isolated in patients receiving home PN is coagulase-negative *Staphylococcus* (CONS), accounting for up to 60% of home PN bacteremias. This is followed by *Enterococcus*, *S. aureus*, and *Candida* sp. Gram-negative bacteria account for 14% to 25% of infections. It is important to
recognize that the management of CVC infections in this patient population is different from most patients. Typically, a suspected CVC infection mandates removal of the catheter, particularly in the inpatient setting. In IF/SBS patients, however, a trial of broad-spectrum antibiotics while leaving the suspected catheter in situ is important in order to preserve as many future access sites as possible. If 48 hours of antibiotics has not demonstrated clinical improvement or if the patient is clinically worsening during the trial period, then removal of the tunneled catheter is warranted. If the suspected organism causing the sepsis is a fungus, earlier removal is recommended.

Metabolic complications generally are related to fluid/electrolyte disturbances and macro- or micronutrient delivery problems. The complexities of management of hyper- and hypoglycemia are beyond the scope of this chapter. However, it is critical to acknowledge that IF/SBS patients often have high-output ostomies or enterocutaneous fistulae, both of which require higher additional water and electrolyte replacements and vigilant attention to the patient’s hydration status. It is known that these patients live in a chronically dehydrated state, and this contributes to a silent renal insufficiency that is not always readily apparent. Blood urea nitrogen (BUN) and creatinine are not reliable indicators of renal function in these patients, as they are often sarcopenic, and these variables will often underestimate the degree of renal impairment. Ament and others at UCLA have previously demonstrated that children with IF who were on TPN had a reduction in yearly GFR that was inversely correlated with chromium concentration in TPN as well as the duration of TPN use. Therefore, we have made it our practice to follow the GFR closely for these patients in the outpatient setting, and our intestinal transplant evaluation process includes a nuclear medicine GFR study to accurately determine the patient’s renal function.

Organ dysfunction is the final stage of PN-related complications. In addition to the renal insufficiency discussed above, other organ systems that can be injured with PN include the skeletal system (osteomalacia, osteopenia, osteoporosis), intestine (bacterial overgrowth, increased permeability, and bacterial translocation), neurologic (memory disturbance), gallbladder (sludge/cholelithiasis/dyskinesia) and liver (steatosis, cholestasis, fibrosis, cirrhosis, and portal hypertension).

IFALD is a well-recognized complication of PN for both children and adults. It is commonly identified by the presence of jaundice, although that
represents an advanced stage of liver disease. More conventional practice has focused on using liver function tests at 1.5 times the upper limit of the reference range, for at least 2 weeks, and in the absence of another cause to define the presence of IFALD. Given the large variation in defining IFALD, incidence estimates are often difficult to obtain. It has been consistently reported, however, that approximately 50% of children on PN for 4 to 12 weeks have cholestasis, but in adults there is a much wider variation in frequency of IFALD, with around 30% to 50% having a mild disturbance of liver function tests and between 2% and 30% becoming cholestatic after a median of 6 months of PN. Nonetheless, it is important to recognize that a large proportion of patients on PN will suffer from some form of liver injury, and the early signs of IFALD must be recognized and treated with adjustment of PN formulas that reduce total calories and increase the carbohydrate:lipid ratios. If allowed to progress, decompensated IFALD can occur very rapidly, and this accounts for the high mortality rate of patients awaiting combined liver and intestine transplants.

**EMERGING PHARMACOLOGIC OPTIONS FOR INTESTINAL FAILURE**

The period of adaptation following the onset of SBS-associated intestinal failure is believed to last approximately 24 months. The process of adaptation occurs through both structural (villous cell hyperplasia, increased crypt depth, and intestinal dilatation) and functional (increased mucosal enzyme activity and reduction of intestinal transit) mechanisms leading to a gradual increase in absorptive capacity. Nutritional (eg, glutamine) and non-nutritional (eg, growth factors) substances have been implicated in promoting this adaptive response. In the last decade, most intestinal failure research has been focused on exploring the potential of these substances as supportive intestinal failure treatment. However, clinical trials so far have not demonstrated reproducible or meaningful clinical benefits with the use of glutamine or growth hormone.

GLP-2 is a 33-amino acid peptide that has shown great promise in helping intestinal failure patients achieve PN independence. Human and animal studies have revealed that dietary fiber and short-chain fatty acids, carbohydrates, and fats are potent stimulators of GLP-2 secretion. GLP-2
exerts a wide variety of effects on the gastrointestinal tract and is a key mediator of intestinal adaptation. In animal studies, GLP-2 treatment induces mucosal growth in the small and large intestine through an increase in crypt cell proliferation and a reduction of villous cell apoptosis. This increase in mucosal mass is accompanied by enhanced functional absorptive capacity. Recent multicenter, placebo-controlled studies of GLP-2 in SBS patients demonstrated meaningful reduction of up to 20% less PN use in patients who received GLP-2. Future studies using GLP-2 in combination with other growth hormones could potentially pave the path toward PN independence for many intestinal failure patients.

AUTOLOGOUS LENGTHENING TECHNIQUES OF THE GI TRACT

The basic principles behind surgical adaptation are to recruit and optimize the surface area of unused intestine in order to improve intestinal function and achieve enteral nutrition. First and foremost, fistulae and ostomies must be closed and bowel obstructions must be surgically relieved. Once this has been achieved, bowel tapering and lengthening procedures can be performed. Prior to embarking on these often-treacherous surgical explorations, it must be deemed that the patient has a reasonable chance to achieve independence from PN and that the remaining bowel length and function will not be better served by transplantation. Several surgical options exist, such as reversed segments, colonic interposition, and nipple valve construction. These techniques have not been widely used or commonly successful. We will primarily focus on the more commonly used non-transplant surgical options including the Bianchi procedure (longitudinal lengthening) and the STEP procedures.

Bianchi Procedure

The Bianchi procedure was first described in 1980 in a pig model. It was then applied to humans, and several published reports became available in the 1990s depicting their results. In brief, the technical conduct of the procedure intends to achieve longitudinal length by dividing the small bowel at either end of a dilated loop. The plane between both leaves of the mesentery is then
developed so as to maintain the blood supply to both of the stapled ends of bowel. A GI stapling device is then passed between both leaves of mesentery and applied to the single, dilated loop of bowel. Once the stapler is fired, the single loop of bowel then becomes two parallel loops of normal caliber bowel, each with its own mesentery. The two new loops of bowel are then sewed to each other in an antegrade, end-to-end fashion forming a “lazy S” configuration (see Fig. 42-2). Several published series of Bianchi longitudinal lengthening procedures have been published and many of the authors were able to reproducibly double the lengths of bowel in their series of patients. With the increased length, patients were able to achieve improved intestinal motility and prolonged transit times. Although most series of patients were small, Weber and others were able to demonstrate complete parenteral independence in many patients along with improved carbohydrate and fat absorption. Although the early results of this procedure were promising, it largely has become of historical value due to complexity of the procedure, the difficulty in predicting which patients would become enterally independent, and the advent of intestinal transplantation.

**FIGURE 42-2** Longitudinal intestinal lengthening. (A) The small bowel is divided at either end of a dilated loop. The mesentery is dissected to create a...
plane along the axis of the intestine between branches of mesenteric blood vessels. (B) The mesentery has two leaves. Arterial and venous branches of mesenteric vessels alternate from one leaf of the mesentery to the other. (C) A gastrointestinal stapling device can be passed between the leaves of the mesentery. (D) When the stapler is fired, the single loop of dilated intestine is divided into two parallel loops. (E) The parallel loops can then be turned in a “lazy S” fashion to approximate the distal end of one loop to the proximal end of the second loop. In this way, the parallel loops are anastomosed end-to-end to reestablish continuity and double the length of the small bowel. In addition, the lengthened segment is then reanastomosed to the normal small bowel or colon proximally and distally (not shown).

**Serial Transverse Enteroplasty**

In 2003, Kim and others introduced a novel technique for bowel lengthening.\(^4^8\) Once again, the general concept was to introduce overall surface area in order to increase mucosal contact with nutrients. With the STEP procedure, however, this was achieved by narrowing the luminal diameter that would result in increased bowel distances between areas of undivided bowel, thus leading to increased transit times. In brief, the dilated segment of small bowel is narrowed by alternate firings of the GI stapling device from the mesenteric and antimesenteric borders of the bowel. This would result in luminal diameters between 1 cm and 2.5 cm and a resultant increase in bowel length (see Fig. 42-3A-C).\(^4^8\) In 2013, Kim and others published their results from the STEP registry data which included 111 patients in 50 centers worldwide. They were able to demonstrate that 47% of patients who were on PN pre-STEP were able to achieve complete enteral nutrition after their STEP procedure.\(^4^9\) The overall mortality in this study was 11%, but it likely reflected the high acuity of the patients who were undergoing surgery as the two main risk factors for death on multivariate analysis were higher direct bilirubin and shorter bowel length.\(^4^9\) Intestinal lengthening procedures have a clear role in patients with intestinal failure. The basic premise is that patient selection is of paramount importance because patients who are jaundiced should likely be considered for transplantation, and lengthening procedures are likely contraindicated.
FIGURE 42-3 The STEP procedure is shown here. A. The dilated intestine is divided from alternating sides using a stapling device thus creating a zig-zag pattern, B. the resultant intestine is shown intra-operatively, and C. the simple calculation of the new functional length of the intestine after STEP is shown as initial length plus the product of the length of each staple cut times the number of cuts. (Reproduced with permission from Kim H, Fauza D, Garza J, et al. Serial transverse enteroplasty (STEP): A novel bowel lengthening procedure, *J Pediatr Surg* 2003 Mar;38(3):425-429.)

INTESTINAL TRANSPLANTATION

ITx marks the final available therapy for patients with IF/SGS who in general have failed PN therapy. The indications are:

1. Patients with permanent/irreversible IF/SBS with one or more life-threatening PN-related complications such as loss of central venous access, recurrent catheter-related bloodstream infections, and/or IFALD.
2. Patients with a poor prognosis for enteral adaptation, such as those with complete loss of midgut, should also be considered early in their onset of IF/SGS for ITx.
3. Patients with poor quality of life, uncontrollable fluid and electrolyte disorders, and chronic abdominal pain while on PN should be considered.
4. Patients with low-grade unresectable malignancies such as gastrointestinal stromal tumors (GISTs) or desmoids may benefit. Likewise, patients with polyposis syndromes may benefit from subtotal enterectomy and transplantation.
5. Lastly, patients with pan portosplenic mesenteric venous thrombosis not amendable to shunting or isolated liver transplantation should be considered. Once patients have been deemed candidates for ITx, a complete multidisciplinary evaluation at a transplant center is carried out to determine eligibility. Specifications for this process vary from center to center and have been outlined in “Assessment of SBS-Associated Intestinal Failure”. Once accepted for transplantation, the patients are listed for the intestinal type of allograft deemed necessary. In general, diseased organs are replaced while functional ones should be retained.
Donor Selection

In general, cadaveric donors of intestinal grafts are often young, healthy individuals who have suffered a catastrophic brain trauma or anoxic brain injury. These donors are a highly selected subset of patients mainly because of the sensitivity of the intestine to ischemic injury. Thus, many of the events surrounding brain death (down time, length of cardiac arrest/cardiopulmonary resuscitation) and peri-donation management (vasopressor requirements) of the donor will often exclude these patients as donors for intestinal grafts.

Donor/Graft Techniques

The donor operation for multiorgan procurements is employed when the team is planning to procure multivisceral grafts. Within the abdominal compartment, preparation for rapid aortic cross-clamp is performed by first cannulating the inferior mesenteric vein for infusion of portal cooling flush both prior to aortic cross-clamp and after cross-clamping/exsanguination has occurred. The infrarenal aorta is encircled and cannulated and the supraceliac aorta is also encircled in preparation for placement of a vascular clamp just prior to exsanguination and cooling with University of Wisconsin solution (ViaSpan®, Barr Laboratories). After these steps and in coordination with the chest teams, the liver, pancreas, and small intestine can be procured either separately or in combination, depending on the recipient’s needs (see Fig. 42-4).
FIGURE 42-4  Diagram demonstrating the graft options resulting from a multiorgan procurement. Divisions at duodenum and jejunum indicate potential levels of transection, both vascular and gastrointestinal. Thus, all organs can be procured either separately or in any combination.

**Intestinal Type of Grafts**

In general, there is little consensus on the terminology regarding allograft type. This chapter utilizes the intestinal graft types as described by the
The graft types are (1) isolated intestinal allograft, (2) liver-intestine allograft, (3) multivisceral allograft, and (4) modified multivisceral allograft. Of note, accessory organs can be easily added to most of the graft types. Accessory organs are the stomach, colon, and kidney. These are discussed separately.

**ISOLATED INTESTINE GRAFTS**

Isolated intestine (I-ITx) grafts contain all or part of the donor jejunoileum. The jejunum is stapled past the ligament of Treitz, and the small mesenteric vessels connecting the proximal mesentery are ligated. In this scenario, the SMA and SMV are used as the vascular pedicles at the root of the mesentery in the recipient operation. If the pancreas is not being procured, the SMA can be lengthened to include a cuff of aorta and the SMV can go up as far as the portal vein (PV) (see Fig. 42-5a). This graft type is indicated for patients with IF/SBS only who have normal foregut and liver function.

**FIGURE 42-5** (A) Demonstrates a jejunoileal graft procured with its vascular pedicle consisting of the SMA and SMV. (B) Demonstrates a liver-intestine (L-ITx) graft procured using the traditional technique; the entire liver and jejunoileal segment is present. The vascular inflow is shown off a cuff of donor aorta. (C) Demonstrates multivisceral (MVTx) allograft. ([A,C]: Reproduced with permission from Moon JI, Tzakis AG: Intestinal and multivisceral transplantation, Yonsei Med J 2004 Dec 31;45(6):1101-1106.)
LIVER-INTESTINE GRAFTS

The original description of this technique was by Grant et al., where this graft included an en bloc liver and intestine only, while the donor pancreas was removed. Today, the most commonly used method for procurement of the liver-intestine (L-ITx) graft is the “Omaha technique.” With this technique, the liver is mobilized using standard techniques. The duodenum is stapled off distal to the pylorus, the pancreas is left wholly intact for biliary drainage, and the entire jejunileum is mobilized and controlled. At completion, the L-ITx graft consists of liver, duodenum, pancreas, spleen, and jejunuleum with the vascular pedicles of a common aorta/celiac/SMA trunk and an intact donor PV and bile duct (see Fig. 42-5b). Liver-inclusive grafts are used in the clinical scenarios where patients have experienced liver failure, as in IFALD coupled with IF/SBS.

MULTIVISCERAL GRAFTS

The multivisceral (MVTx) graft is very similar to the L-ITx graft described above. The stomach is most commonly included in this allograft type. During the procurement operation, rather than dividing at the level of the pylorus, the esophagus is transected above the GE junction. At completion, the organ complex consists of liver, duodenum, pancreas, spleen, and jejunuleum with or without the stomach. Vascular inflow is the same as described above for the L-ITx graft (see Fig. 42-5c). This allograft is used in patients with disease of both the foregut and midgut who also have irreversible IFALD.

MODIFIED MULTIVISCERAL GRAFTS

Modified multivisceral MMVTx grafts are basically the same as the MVT except that the liver is not included in the complex. This allograft is used in patients with disease of both the foregut and midgut but where native liver function is preserved or salvageable.

Accessory Organs

As noted above, the stomach can be added onto the MVT or MMVTx allografts largely in patients who have motility disorders involving the
stomach. Of note, due the fact that a vagotomy is performed in the donor, a pyloroplasty is required in this scenario. Alternatively, the stomach transplant can be omitted and thus a partial or subtotal gastrectomy is performed with the use of a Roux-en-Y gastrojejunostomy for final GI reconstruction.

Colon-inclusive transplantation was initially deemed to be higher risk with worse outcomes. However, subsequent experiences demonstrated that colon inclusion can be accomplished without a higher rate of sepsis or graft loss. In the donor, rather than transect the intestine at the terminal ileum, the line of transection can occur in the mid-transverse colon (beyond middle colic vessels) or more distal. Inclusion of the colon is indicated for patients without significant remnant native colon, as it has been shown to improve fluid management post transplant.

Concomitant kidney transplantation can also occur in patients with poor chronic renal function deemed candidates for such a transplant. The kidney allograft can be included en bloc with the visceral organs. We most commonly keep the right kidney intact, with the renal artery included in the aortic cuff and the renal vein included in the inferior vena cava (IVC). In this manner, only ureteral reimplantation is required in the recipient.

**Recipient Operation**

The recipient operation can vary considerably between patients; thus, we briefly touch upon the major components of the recipient operation. As we have noted throughout this chapter, *vascular access* is of paramount importance with these patients. Preoperative mapping with a magnetic resonance venogram (MRV) is usually performed during the initial evaluation, and this is often necessary to help guide the anesthesiologist during CVC placement. Central access above the diaphragm is usually necessary both because of substantial blood loss encountered during the organectomy in a hostile abdomen and also because large-bore peripheral IV access is generally not possible in these patients.

*Exposure* is the key to any operation. In a hostile abdomen, achieving exposure is often treacherous, and an adequate incision followed by extensive adhesiolysis is generally necessary before organectomy can proceed. For liver-inclusive grafts, a bilateral subcostal and vertical incision is necessary with extension of the midline incision to below the umbilicus. For patients
who are not receiving the liver as part of their grafts, a midline laparotomy incision is sufficient. With these incisions, optimal exposure to achieve venous outflow into the portomesenteric circulation and also to restore gastrointestinal continuity can be established.

Recipient organectomy is variable depending upon the organ(s) being transplanted. In general, the I-ITx recipient undergoes mobilization of the remnant jejunooileum. This is resected while leaving behind a suitable length of jejunum to perform jejunoojejunostomy between donor and recipient jejunum as well as distal colon to perform jejunocolostomy between donor jejunum and recipient colon. Vascular inflow and outflow was discussed for each type of grafts above. However, it should be mentioned that during the recipient operation liberal use of aortic conduits should be used. Generally, donor iliac or donor aorta can be used to create a conduit at the recipient infrarenal aorta that will be then be sewn to the allograft during implantation. When en bloc organs are procured, the suprahepatic IVC of the donor graft serves as the venous outflow. Biliary reconstruction requirements are variable depending on the graft used. In liver-inclusive grafts procured using the Omaha technique or as MVTx grafts, biliary anastomosis is not needed. This is followed by restoration of intestinal continuity. Again, the grafts being used as detailed previously will dictate the targets for intestinal anastomosis. Of importance, however, is the critical step of creating intestinal continuity along with an ileostomy to allow for allograft surveillance with biopsies in the perioperative period. Enteral feeding tube placement is the next surgical step, and this can be in the form of a Stamm gastrostomy in patients who do not receive a stomach, or as a jejunostomy tube into the transplanted intestine. Finally, abdominal wall closure is often complex, since these patients have had multiple previous operations and primary fascial closure is often difficult to achieve. In order to provide a tension-free closure, the liberal use of prosthetic materials as a temporary closure device while abdominal wall and bowel edema subsides is often the best strategy. A second-look laparotomy can then be performed and a definitive closure can be performed at that time either primarily or with permanent mesh (see Fig. 42-6).
FIGURE 42-6 Diagrams demonstrating an isolated intestinal graft after implantation (A), and liver-intestinal graft with inclusion of the whole pancreas (B) and a multivisceral graft (C). The vascular anastomoses are indicated. Abbreviations: SMV, superior mesenteric vein; PV, portal vein; SMA, superior mesenteric artery; IVC, inferior vena cava.

COMPLICATIONS OF INTESTINAL TRANSPLANTATION

Surgical complications after ITx can be broken down into postoperative-, endoscopic-, or vascular access–related. The postoperative complications have evolved over time. Biliary complications are no longer a major problem given that we no longer perform a complete hilar dissection as was originally described by Grant et al.\(^8\) Thus, this has left us mainly with intestinal perforation, mechanical obstructions, anastomotic leaks, intra-abdominal abscesses, chylous ascites, ostomy-related complications, and vascular complications.\(^{50}\) These complications are all life-threatening in an immunosuppressed patient, and a low threshold for reexploration should be maintained as the clinical presentation can often be insidious.

Endoscopic complications are not uncommon in the intestinal transplant patient. These patients are regularly monitored for rejection in the postoperative period and they are thus at risk for bleeding, hematoma causing obstruction of the bowel lumen, perforation, and stomal disruption.\(^{24}\) In a
recent review of 1770 endoscopic procedures in intestinal transplant recipients, the rate of procedural complications, including but not limited to bleeding and perforation, was 1.8%.\textsuperscript{56} Similarly, vascular complications often persist in the post-transplant period. This often presents a challenge since most patients who have a functional graft have not completely weaned off of PN in the postoperative period. Some groups have reported up to a 15% incidence of patients experiencing thrombosis of their central veins that have required balloon angioplasty to maintain access following transplantation.\textsuperscript{57}

Medical complications after ITx are largely related to infectious and immunosuppression-related issues. Recipients of intestinal transplants are at major risk for infections because the transplanted organ represents a reservoir of pathogens. In the immediate perioperative period, the source of infection is often from catheter-related bacteremia, anastomotic dehiscence, or intra-abdominal fluid collections. In long-term patients, urinary tract infections, pneumonia, and catheter infections predominate as the causes for infections. However, it should be noted that patients with marginal graft function often are subject to bacterial translocation with resultant bacteremia. Thus, prevention of bacterial overgrowth with scheduled administration of oral antibiotics can often be useful to prevent recurrence of bacteremia.

Immunosuppression-related complications are vast in number and beyond the scope of this chapter. However, it is important to recognize that there is a broad spectrum of complications that occur as a result of over- or under-immunosuppression.\textsuperscript{58} On the one hand, acute rejection is almost invariable for most intestinal transplant recipients, especially in young patients or those who are noncompliant with their immunosuppression regimen. At the opposite end of the spectrum, lymphoproliferative disorder (PTLD) can occur in patients who are over-immunosuppressed or have received induction agents at the time of transplant such as antithymocyte globulin (ATG) or lymphocyte-depleting agents. Given the presence of lymphoid-rich tissue in intestinal grafts, graft-versus-host disease (GVHD) can occur in up to 5% of patients and is clinically marked by diarrhea, ulceration of oral mucosa, and skin rash.\textsuperscript{24} It is this balancing act of over- versus under-immunosuppression that calls for very close monitoring, even when patients are remote from their operations, as these complications can arise over the entire course of a transplant recipient’s life.
SUMMARY AND FUTURE DIRECTIONS

ITx has evolved since the initial attempts in the 1960s. Our knowledge of immunology, experience with surgical techniques, and perioperative care has improved substantially and this has afforded a 1-year graft survival of approximately 80%. The field of ITx depends on the contributions from a multidisciplinary team and strong support from an intestinal rehabilitation program that can bridge IF/SBS patients toward transplant. Aggressive rehabilitation programs that focus on minimizing complications from PN, re-establishing GI continuity, maximizing enterocyte mass via STEP procedures, and optimizing macro- and micronutrient delivery all contribute to successful patient outcomes. Future directions that will focus on tolerance induction, prevention of PTLD, and tissue engineering will help pave the path for intestinal transplantation and hopefully minimize the morbidity associated with immunosuppression.

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DIVERTICULAR DISEASE AND COLONIC VOLVULUS

Timothy Eglinton • Frank A. Frizelle

Diverticular disease and colonic volvulus are common benign colonic conditions that can cause patients significant symptoms, impair of quality of life, and on occasion lead to fatal outcomes without treatment. Management at times can be challenging as decisions for surgical intervention must be carefully balanced against the patient’s relative procedural risks and comorbidities, which also can be significant. In this chapter, we discuss the current understanding of these 2 pathologies.

DIVERTICULAR DISEASE

Colonic diverticula are the most common structural abnormality of the bowel and constitute the fifth most costly gastrointestinal disorder in Western society.\(^1,2\) An acquired condition, diverticula usually affect the sigmoid colon in Western societies, but they are also found on the right colon in countries with diets rich in fiber, especially in Asia. The prevalence of clinically apparent diverticular disease has increased over the past century,\(^3\) which probably reflects both an increase in detection and an aging population. Until 30 years ago, the proportion of patients requiring surgery or dying from
diverticular disease was decreasing\textsuperscript{4}; however, over the past 20 years, the rates of hospital admission and surgical intervention have increased, while inpatient and population mortality rates from diverticular disease have remained unchanged.\textsuperscript{5}

Colonic diverticulum is an acquired condition with increased prevalence with increasing age. It affects fewer than 10% of people in their fifth decade of life, increasing to around 50% to 66% in their ninth decade.\textsuperscript{6} Most patients with diverticulosis do not require surgery; however, complications of diverticular disease may require surgery. Such surgery can be challenging, and good outcomes rely on timely and appropriate intervention.

The terms used include diverticulum (diverticula—plural); diverticulosis, which indicates asymptomatic diverticula; diverticulitis (simple or complicated), or diverticula with inflammation; and diverticular disease, which is diverticula with or without inflammation.

**History**

Diverticular disease was initially described by Littré in 1700 as saccular outpouchings of the colon.\textsuperscript{7} Cruveilhier is credited with the first clear and detailed description of the pathogenesis of diverticulitis and complicated diverticular disease.\textsuperscript{8} In 1899, Graser introduced the term “peridiverticulitis” and suggested that diverticula were caused by herniation of colonic mucosa through areas of penetration of the vasa recta. This is now well established as the pathogenesis of colonic diverticulosis.\textsuperscript{9} In contrast, the mechanism for diverticulitis was not identified until 1904 by Edwin Beer.\textsuperscript{10} This seminal work on the pathophysiology of diverticular disease reviews the medical literature on diverticular disease at the turn of the 19th century. Beer summarized the use of cadaveric and animal experiments to identify diverticula associated with colonic wall blood vessels and ascribes the cause of diverticulitis to hard fecal matter lodged within the diverticulum.\textsuperscript{11} He described the ensuing pathologic processes of mucosal ulceration, acute inflammation, abscess formation, colonic perforation, and fistulation. Beer also describes the process of cicatricial contraction caused by marked “connective tissue growth.” Beer also succinctly summarizes 18 case reports into 6 clinical scenarios, including diverticula that produce stenosis of the sigmoid or upper rectum, diverticula that lead to perforation into the
peritoneum, diverticula that lead to abscesses or localized peritonitis in the left iliac fossa, diverticula that lead to perforation into the urinary bladder, diverticula that are densely adherent to the bladder, and diverticula and carcinoma. He proposed that impacted fecal matter at the neck of the diverticulum caused inflammation and subsequent abscess and fistula formation.

Moynihan\textsuperscript{12} reported a case of peridiverticulitis in 1907 and underlined the difficulties in distinguishing diverticular disease from malignancy. Telling and Gruner’s classic paper describing complex diverticular disease was not published until 1917.\textsuperscript{13} At this time, the prevalence and pathophysiology of diverticular disease were well recognized, as were the complications, including acute diverticulitis, abscess, fistula, perforation, and obstruction.

The development of radiologic imaging of the large intestine was important in establishing a diagnosis and documenting the extent of diverticular disease.\textsuperscript{14} In 1914, De Quervain and Case were the first to demonstrate colonic diverticula with x-rays.\textsuperscript{15,16}

**Etiology**

Diverticular disease is a disease of Western populations. A number of studies have shown an increase in incidence over the past 30 years.\textsuperscript{3,5} Migrant studies likewise confirm an increase in incidence when populations move to a Western country. There is a widely held view that fiber content of food is important and that the high intraluminal pressure associated with low-fiber diets precipitated by colonic compartmentalization causes an unsustainable increase in tension within the bowel wall. This is compounded by the hyperelastosis and altered collagen structure seen in the colon due to aging.\textsuperscript{17,18} Both mechanisms ultimately lead to a loss of bowel wall integrity and the formation of diverticula. Exercise and a reduction in the intraluminal pressure associated with a high-fiber diet may be protective.\textsuperscript{19}

High intraluminal pressures are generated because of colonic motility. Colonic motility is complex and not easily studied. The most common motor patterns are tonic segmenting and rhythmic contraction. Tonic segmentation creates stationary narrow rings that appear as haustral markings. Their purpose is to slow the fecal stream and to permit water absorption and
electrolyte exchange. Infrequent propulsive peristaltic contractions move fecal matter in a caudal direction; these occur around 6 times a day.\textsuperscript{20}

The alteration in pressure caused by these movements has been implicated in the pathogenesis of colonic diverticulosis. Several groups have studied colonic motility with intraluminal manometry in humans and animals. Most studies agree that there is increased phasic pressure activity, but this relates more to the presence of symptoms rather than diverticula. The results, however, are heterogeneous, principally because of methodologic differences, in particular relating to bowel preparation and pressure sensors.\textsuperscript{21} It may therefore be unreasonable to draw firm conclusions from these investigations.\textsuperscript{22}

More generalized alterations in colonic motility have been implicated in the pathogenesis of colonic diverticular disease. In vitro and in vivo studies, however, are conflicting. Some demonstrate an absence of slow-wave activity (favoring nonpropagating contractile activity), and some demonstrate unimpaired or increased slow-wave activity.\textsuperscript{23,24} Others have demonstrated an increase in fast-wave activity, which persists after resectional surgery.\textsuperscript{25} The exact relevance of these myoelectric changes remains uncertain.

Diverticulosis is a Western disease that has a striking geographic distribution. The disease is rare in rural Africa and Asia with the highest prevalence seen in the United States, Europe, and Australia.\textsuperscript{26} Within a single country, the disease incidence can vary depending on ethnicity.\textsuperscript{27} Urbanization can also increase diverticular disease incidence, possibly attributable to a dietary change.\textsuperscript{28,29} The incidence of complicated diverticular disease also seems to be increasing.\textsuperscript{30}

Diverticular disease in Asian patients is often right-sided with manifestations early in life and is often multiple. The reasons for this variation are unknown; however, it has been suggested that both diet and elastin/collagen differences may play a role.\textsuperscript{31}

**Morphologic Features**

Colonic diverticula are false diverticula most commonly found in the sigmoid colon (95%). The sigmoid colon is the exclusive site in about 50%, and the entire colon is involved in just 5%. The muscular colonic wall is composed of both longitudinal and circular layers. The circular layer of the muscularis
propria forms a continuous sheet of muscle throughout the large bowel. The longitudinal layer forms 3 discrete condensations called taeniae; 1 of these is adjacent to the mesentery while the other 2 are antimesenteric. The taeniae coalesce to form an enveloping muscular layer in the rectum. Much of the colonic wall is therefore devoid of longitudinal muscle, and it is in these areas that diverticula form. Herniations of muscularis mucosa occur between the taeniae along the arteries (vasa recta) that penetrate the muscle wall en route to the submucosa and mucosa (Figs 43-1 and 43-2).

**FIGURE 43-1** Relationship of diverticulum and vasa recta.
Many studies have demonstrated a change in the histologic structure of the muscularis propria in diverticular disease. In a classic study, Whiteway and Morson\textsuperscript{17} found the muscle cells to be normal with no evidence of hyperplasia or hypertrophy, but both layers were thickened. They demonstrated excessive amounts of elastin in the taeniae but not in the circular muscle.\textsuperscript{17} Repeated intermittent distension of the colon can result in increased synthesis of connective tissue components.\textsuperscript{32} It may be that the Western diet with its lower fecal load only intermittently distends the bowel wall and encourages elastin deposition.

The importance of collagen and elastin types in the colonic wall is increasingly being recognized. Elastin deposition, termed “elastosis,” explains the contracted and thickened appearance of the diverticulum-affected colon. The taeniae shorten, and because of fascial linkage between the longitudinal and circular muscles, the colonic wall looks like a concertina. Thickened circular muscle folds project into the lumen, causing a decrease in caliber. The mesocolon is also foreshortened, possibly as a result of chronic inflammation. Other studies have suggested that the type of collagen may be
important. One study has shown that in the bowel sections of patients with diverticulitis, there were decreased levels of mature collagen type I and increased levels of collagen type III with a resulting lower collagen I:III ratio. The expression of matrix metalloproteinase 1 was reduced significantly in the diverticulitis group. These findings support the theory of structural changes in the colonic wall as one of the predisposing pathogenic factors for the development of diverticula (Fig. 43-3A and 43-3B). In those with certain connective tissue diseases, such as Marfan and Ehlers-Danlos syndromes, diverticular disease is a common association.
FIGURE 43-3  A. Sigmoid colon with diverticula. B. Mucosal view of colonic diverticula.
Diverticulitis always starts with a microperforation, leading to peridiverticulitis. This is instigated by either a rise in intraluminal pressure and/or erosion by inspissated feces. Nonresolution of this initial injury leads to complications of diverticulitis.

**Presentation**

Given the high incidence of diverticulosis, it is surprising that clinical manifestations are relatively infrequent. Many patients are unaware that they have colonic diverticula until they develop acute symptoms or when diverticulosis is found incidentally during colonic investigations. Typically an acute attack of diverticulitis begins with lower abdominal pain that then localizes to the left iliac fossa. An inflamed sigmoid colon can lie against the dome of the bladder or the cecum, mimicking a urinary tract infection or appendicitis. Fever, tachycardia, and a leukocytosis accompany the acute attack. The inflammatory response starts at the site of a blocked diverticulum, and bacterial proliferation eventually leads to abscess formation. Minor episodes may be self-limiting, but an abscess can develop and then rupture into the abdomen causing a purulent peritonitis. More rarely, feculent peritonitis occurs when a diverticulum ruptures freely into the peritoneum. \cite{34-41}

Physical examination will often reveal peritonitis localized to the left iliac fossa or suprapubic area; a palpable mass is not uncommon.

The differential diagnosis includes appendicitis, segmental ischemic colitis, colorectal cancer, inflammatory bowel disease, gastroenteritis, and irritable bowel disease.

In the absence of complications, patients with acute diverticulitis are best managed conservatively with antibiotics. Generalized rigidity suggests purulent or fecal peritonitis, and early surgery is required in this situation. Once fluid and electrolyte resuscitation has begun, an emergency laparotomy or laparoscopy with an appropriate colonic resection should be performed.

Often, diverticular disease presents in a more indolent manner with nagging left iliac fossa pain, abdominal distension, and a change in bowel habit. In the course of investigations to exclude colon cancer, diverticular disease may be discovered by computed tomography (CT) colonography, or colonoscopy (Figs 43-4, 43-5A, and 5B). In the majority of these patients,
education about the natural history of the disease with advice on dietary modification and supplementary written information will suffice. A very limited number of patients who continue to have symptoms despite long periods of medical management may benefit from surgery in the absence of other specific complications of the disease; however, determining the contribution of symptoms from diverticular disease and associated conditions such as irritable bowel syndrome can be difficult. These patients often have persisting symptoms following surgery.

**FIGURE 43-4** Left colonic diverticula on double-contrast barium enema (arrows).
FIGURE 43-5  CT axial view of sigmoid diverticula.

COMPLICATIONS
**Free Perforation.** Feculent peritonitis is usually associated with toxemia and signs of generalized peritonitis. These patients will require an immediate laparotomy, resection, and diversion. Mortality rates for emergency operations have remained unchanged at 12% to 36% for the past 20 years and are most often affected by the patient’s underlying fitness for surgery.

**Fistula.** An inflamed segment of sigmoid colon can adhere to a number of intra-abdominal structures or to the abdominal wall. A fistula may arise spontaneously as a result of the inflammatory condition itself or as a result of surgical intervention. It is more common in males, in those with previous abdominal surgery, and in immunocompromised patients. Diverticular fistulas can drain either internally or externally. Often, these fistulas are single tracts, but in about 8% of patients, they are multiple. Rare sites of fistulous involvement include the ureters, other colonic segments, and stomach.

**Colocutaneous.** Occasionally, a paracolic diverticular abscess will discharge spontaneously through the abdominal wall, causing a colocutaneous fistula. More often, a fistula will result from incision and drainage of a pointing paracolic abscess or from a drain placed under radiologic control. A fistula can arise from a leaking colonic anastomosis in patients who have undergone resection for diverticular disease.

**Colovesical.** This is the most common fistula, accounting for about two-thirds of diverticular fistulae. It is more common in men because in women the uterus is interposed between the bladder and the colon. A relatively mobile sigmoid colon becomes adherent to the dome of the bladder and a communication develops. Patients present with recurrent urinary sepsis, urgency, frequency, and pneumaturia. Fecaluria is uncommon. Cystoscopy sometimes identifies an area of inflamed transitional epithelium but is more useful to exclude bladder cancer. A double-contrast enema or CT colonography provides a useful map of the anatomy and in some cases can confirm the presence of a fistula. Caution should be exercised when using barium in an acute situation to avoid peritoneal contamination.

**Coloenteric.** Small bowel can become adherent to an inflamed diverticulum-affected colon. Fistulas form when an abscess discharges through the small bowel wall. This may be asymptomatic.
Colovaginal. This is a particularly debilitating fistula. The patient may pass flatus and feces through the vagina and suffer recurrent vaginal infections. Colovaginal fistulas usually only occur if a previous hysterectomy has been performed. Barium studies of both the bowel and the vagina or pelvic magnetic resonance imaging (MRI) usually can confirm the diagnosis. They are also helpful to exclude colonic malignancy as a cause; however, an examination of the vagina may also be required to exclude the rare possibility of a gynecologic malignancy.

Single-stage operative resection with primary anastomosis and repair of the contiguous organ can be performed in most circumstances. Interposition of the pedicalized greater omentum between the anastomosis and the site of the fistula is a useful adjunct in preventing recurrent fistula formation.

Bleeding. Severe hemorrhage from diverticular disease is rare (5%). However, distinguishing diverticular bleeding from other causes can be a diagnostic challenge, particularly because diverticular disease is so prevalent. In elderly patients, angiodysplasia is the most common colonic cause of rectal bleeding. Taken together, bleeding from angiodysplasia and diverticula account for 90% of cases of severe lower intestinal hemorrhage. In diverticular bleeding, the penetrating vasa recta that has led to the development of the diverticulum is easily eroded as it is only separated from the bowel lumen and its contents by a thin layer of mucosa. On histology, there is thinning of the media and thickening of the intima of the vasa recta with rupture of the vessel usually at the dome of the diverticulum. There usually is no inflammation associated with the bleeding diverticulum.

Diverticular hemorrhage presents with abrupt passage of large-volume bright or dark red blood per rectum and may be associated with lower abdominal pain probably related to colonic distension. Most diverticular bleeding occurs from left-sided diverticula except in patients of Asian ethnic origin, in whom it is more common to find the bleeding occurring on the right side. Diverticular bleeding is more common in those on nonsteroidal anti-inflammatory drugs (NSAIDs). Colonoscopy in situations of large-volume bleeding is considered futile if not dangerous. CT angiography is now considered the most useful diagnostic test as it more readily localizes the site of bleeding should the bleeding rate exceed 0.5 mL/min. Formal mesenteric angiography to embolize the segmental vessel is then undertaken with good bleeding control and low associated complications (Fig. 43-6). Failing
this, other techniques to control or localize the bleeding site include vasopressin injection or methylene blue. A more sensitive test for colonic bleeding is a radiolabeled red blood cell scan or technetium-99m–labeled sulfur colloid (>0.1 mL/min), but accuracy in localizing the bleeding site is not as good. Colonoscopy can be used before a laparotomy or as an adjunct with the abdomen open if all else fails in a patient who continues to bleed. It is useful in an attempt to localize and control the bleeding or to minimize the amount of colonic resection. It is also important to note that in these situations a preoperative gastroscopy is mandatory to exclude an upper gastrointestinal tract source of bleeding. Most diverticular hemorrhage ceases spontaneously (70%-80%), with rebleeding rates of 22% to 38%. High-dose barium impaction therapy has been suggested to reduce the risk of rebleeding, and a recent randomized controlled trial with medium-term follow-up supported its efficacy. CT colonography or colonoscopy in patients who have stopped bleeding is useful to exclude malignancy, particularly in those with smaller volume bleeding, with associated suspicious symptoms, or with a significant personal or family history of cancer.
Obstruction. Obstruction due to diverticular disease accounts for 10% to 20% of large bowel obstructions (LBOs) in Western society. Diverticular disease causes colonic obstruction through either luminal stenosis as a result of wall edema on top of the already thick-walled, fibrotic colon or extrinsic compression from an abscess (Fig. 43-7). Often the obstruction is incomplete. Small bowel obstruction can occur if a loop of small bowel becomes adherent to the inflamed sigmoid colon. The diagnosis is usually apparent from the patient’s history. Radiologic confirmation either by contrast enema or by CT with oral and rectal contrast should be obtained. Caution is wise in those with questionable underlying active diverticulitis particularly if complicated by localized perforation. Direct visualization and histologic exclusion of malignancy are mandatory but at times difficult.
Management of colonic obstruction in this setting depends on the mode of presentation and the medical fitness of the patient. An insidious onset is characterized by pain, increasing constipation, and the passage of ribbon-like stools. The majority of patients, however, will present acutely with a classic LBO. The surgical options include a Hartmann resection and resection with primary anastomosis or rarely with a diverting loop ostomy. In patients deemed unfit for surgery, the endoscopic or fluoroscopic deployment of a colon stent is a useful alternative procedure with a high clinical success rate.

Abscess. Abscess formation is the most common complication of acute diverticulitis. It occurs when the center of the inflammatory mass or phlegmon becomes necrotic. The patient presents with worsening abdominal pain, undulating fever, leukocytosis, and raised inflammatory markers. A mass is often palpable in the left iliac fossa or suprapubic region. It may also be felt transvaginally or transrectally. The most common site for a diverticular abscess is in the sigmoid mesocolon, although a variety of unusual presentations have been described. A significant number of abscesses are detected radiologically on CT or ultrasound scanning. Most small (<5 cm) pericolic abscesses can be treated medically with bowel rest and antibiotics. CT or ultrasound-guided drainage is indicated for larger or unresolving abscesses via a percutaneous approach when accessible. Alternatively, these abscesses may also be drained transanally or transvaginally depending on their location. This is successful in up to 90% and will allow subsequent observational management or a single-stage resection. Factors that limit success with this management include abscesses that involve enteric fistulae or multilocular collections especially those containing solid feces. More recently, laparoscopic drainage has been taken up with enthusiasm by several groups with some promising results.
FIGURE 43-8 Sigmoid diverticulitis complicated by a paracolic abscess (with a percutaneous drainage tube in situ).

**Giant Colonic Diverticulum.** Giant colonic diverticulum (GCD) was first described in 1946 by Bonvin and Bonte in the French literature. The first radiologic description was by Hughes and Greene in the American literature in 1953. Various names have been used to describe GCD, including solitary air cyst, giant air cyst, giant gas cyst, encysted pneumatocele, colonic pneumocyst, and giant diverticulum. The variety of names highlights the fact that there has been no clear definition or a single accepted name for these poorly defined lesions that present as large gas-filled cysts attached to the colon (diverticulum). GCD are rare clinical entities with just over 100 cases reported. The age at presentation is comparable to that of patients with conventional diverticular disease. Abdominal pain is the most common symptom, affecting 70% of patients, while 10% are asymptomatic. The most
common physical finding is an abdominal mass, affecting 60% of patients, while 4% have normal physical examinations. Plain abdominal radiology is usually diagnostic of GCD, but CT is often obtained to fully identify the anatomy. Treatment is recommended early, preferably soon after presentation, because of the high complication rate. Surgical treatment may either require a diverticulectomy or segmental resection, and the outcome is usually good.69

**Cancer.** There is little evidence to support an association between diverticular disease and colorectal cancer; however, a recent population-based, case–control study from Sweden identified a causal association between sigmoid diverticulitis and a long-term increased risk of left-sided colon cancer.42

**Investigations**

The spiral CT scan has changed the investigation of acute diverticular disease with sensitivities of 90% to 95%. Although it is debatable whether CT alters disease management in minor diverticular disease, it is invaluable in excluding other causes of abdominal pain and documenting the extent of extraluminal disease. In circumstances in which access to CT is limited, a water-soluble contrast enema study may show mucosal thickening, edema, irregularity, and occasional extravasation of contrast (Fig. 43-9). Sensitivity of a contrast enema study is high.70 Any free perforation is usually contained in an abscess cavity. Contrast enemas are particularly useful for demonstrating the presence and course of an enteric fistula. Barium should be avoided in the emergency setting, as the consequences of barium-induced peritonitis are catastrophic.
FIGURE 43-9 Localized perforation with contrast extravasation into abscess cavity as demonstrated on double-contrast study.

The real advantage that CT scanning affords, in addition to confirmation of the diagnosis, is to direct the treatment of complicated diverticular disease.\(^{71-73}\) Radiologically guided drainage of diverticular abscesses is a useful adjunct to medical management, and can, if successful, avoid the requirement for emergency surgery (see Fig. 43-8).

The role of ultrasound scanning in patients suspected of having diverticular disease has been confined to the treatment and follow-up of diverticular abscess. It is highly operator-dependent, but it can be used to insert drains and to measure the response of the abscess to drainage.

It was traditional practice following resolution of the first episode of diverticulitis to assess the colon for extent of disease and to exclude colorectal malignancy. This can be undertaken with colonoscopy, CT colonography, or barium enema. Care must be taken to wait for full resolution of the attack as an inflamed colon is easy to perforate; also, at times colonoscopy may be very difficult or impossible due to inflammatory adhesions. Colonoscopy generally underestimates the extent of the disease. Recent evidence has challenged the need for routine colonoscopy following an attack of uncomplicated diverticulitis diagnosed by a good-quality CT of
the abdomen. The yield of colorectal cancer in this setting is equivalent to or lower than that in asymptomatic individuals undergoing screening colonoscopy. Examination of the colon remains mandatory after complicated diverticulitis, after a clinical diagnosis of only diverticulitis, or in the presence of any other symptoms suggestive of colorectal cancer or another alternative diagnosis.

Other tests available that may be useful in assessing fistulous disease include MRI scans, cystoscopy, fistulogram, vaginogram, or vaginoscopy.

**Classification of Diverticulitis**

The Modified Hinchey classification is a useful grading system for diverticulitis. More recently, various modifications of the Hinchey classification have been proposed to further subclassify these stages, and these are amalgamated in Table 43-1. Stage 0 is clinical, mild diverticulitis without imaging information. Stage I has been subdivided into stage Ia, which is pericolic inflammation, and stage Ib, which is diverticulitis associated with pericolic abscess. Stage IIa is distant abscess amenable to percutaneous drainage. Stage IIb is complex abscess with or without fistula. Stages III and IV are the same as for the original Hinchey staging.

**TABLE 43-1: CLASSIFICATION OF DIVERTICULITIS**
Management

ACUTE UNCOMPLICATED DIVERTICULITIS

The majority of patients with acute uncomplicated diverticulitis are managed conservatively with intravenous antibiotics, and 95% improve without requiring acute surgery.\textsuperscript{78} The antibiotic should target gram-negative rods and anaerobes, especially \textit{Bacteroides} species. A combination of metronidazole and ciprofloxacin or a broad-spectrum antibiotic such as meropenem or amoxicillin and clavulanate (Augmentin) is most commonly used.\textsuperscript{79} There is, however, quite a variation in the treatment regimen used among clinicians, and there is no specific regimen that has been shown to be superior.\textsuperscript{80} A recent randomized trial called into question the need for antibiotics at all in acute diverticulitis, finding no difference in resolution rates or progression to complications in patients treated with or without antibiotics.\textsuperscript{81} Despite this, antibiotics will remain the standard treatment in most centers until further evidence becomes available.

The decision to operate should be made at a senior level, as the actual number of patients who require resectional surgery for diverticular disease is small.\textsuperscript{82} The increasing use of interventional radiology and laparoscopic surgery has impacted on how diverticular disease is currently managed. This is coupled with a trend to not perform any resectional surgery but, when necessary, to do so with a primary anastomosis in patients presenting with

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Clinical mild diverticulitis without imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia</td>
<td>Pericolic inflammation</td>
</tr>
<tr>
<td>Stage Ib</td>
<td>Diverticulitis with associated pericolic abscess</td>
</tr>
<tr>
<td>Stage IIa</td>
<td>Diverticulitis associated with distant abscess (retroperitoneal or pelvic) amenable to percutaneous drainage</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>Diverticulitis associated with distant abscess (retroperitoneal or pelvic) that is complex and/or associated with a fistula</td>
</tr>
<tr>
<td>Stage III</td>
<td>Diverticulitis associated with purulent peritonitis</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diverticulitis associated with fecal peritonitis</td>
</tr>
</tbody>
</table>
acute uncomplicated diverticulitis.

**ACUTE COMPLICATED DIVERTICULITIS**

Operative indications include free perforation with peritonitis, abscesses not able to be managed conservatively, fistula, and obstruction. The operative rate for complicated diverticulitis overall in the past has been between 19% and 55%. Complicated diverticulitis has been shown by some to be associated with high rates of recurrent complications and high rates of mortality. The mortality in some reports approaches 40%, especially in immunocompromised patients, and similarly, in those with an American Society of Anesthesiologists score of ≥3, there is a mortality rate of up to 28%.

When either an abscess or a diverticulum ruptures into the peritoneal cavity, widespread bacterial contamination ensues with resultant generalized peritonitis. Surgery is principally directed at controlling peritoneal sepsis and should be tailored to each situation. A conservative approach can be taken with elderly and medically unfit patients who are unlikely to survive surgical intervention. The combined use of appropriate antibiotic therapy and regular review is surprisingly successful in this cohort, even in the presence of a pneumoperitoneum.

In patients who are fit for surgery, a period of vigorous resuscitation and antibiotic therapy is still warranted. Even in the face of advanced peritoneal signs, a number of patients will respond to these measures and avoid the requirement for surgery, and others who come to surgery will be in a better condition to withstand the physiologic trauma of surgery. Serial clinical observation is of greatest benefit when pursuing this course. If there is no initial improvement in 8 hours or sustained improvement over 24 hours, then the patient should be recommended to have surgery.

The operative approach is dictated by the findings and condition of the patient. The most common approach is resection of the affected segment of bowel, usually the sigmoid colon, with or without anastomosis. Historically, 3-stage procedures were performed with a defunctioning stoma, followed by resection of the sigmoid, and finally closure of the stoma at a third procedure. This approach was abandoned with a recognition that resection of the affected colon is associated with a lower morbidity and up to 3 times less mortality compared with nonresection procedures. This focused the aims
of surgery on removal of the source of sepsis and toileting of the abdominal cavity.

The development of laparoscopic surgery once again challenged the necessity of resection with the introduction of laparoscopic lavage and drainage for complicated diverticulitis. The first prospective report of this approach in 2008 documented good results in Hinchey stage III disease. The technique involves laparoscopic lavage with drain placement with or without closure of the perforation. This avoids emergency resectional surgery and its associated morbidity and mortality, as well as that from stoma formation and reversal. The promising results from early series led to a number of randomized trials performed predominantly in Europe. Emerging results from these trials have been mixed but generally do not lend strong support to the use of laparoscopic lavage. Two studies suggested increased complication rates in the laparoscopic lavage group compared with the resection group. In contrast, a third study did demonstrate reduced requirement for reoperation in the laparoscopic lavage group. All the trials excluded Hinchey stage IV peritonitis from laparoscopic lavage so there is no doubt this severe disease still mandates resection. The data from trials of Hinchey stage III disease will continue to mature, but in the interim, it appears the previously held principle of surgical resection of the diseased segment should be upheld in the majority of patients with perforated diverticulitis requiring emergency surgery.

The amount of resected tissue depends on the extent of the diverticular disease. At the time of the initial acute surgery, the inflamed bowel needs to be resected. The extent of this resection depends on whether a primary anastomosis is being undertaken or a Hartmann procedure is being performed. When bowel continuity is restored after a Hartmann procedure, total sigmoid colectomy plus removing all of the diverticula bearing colon and a rectal anastomosis has been shown to reduce the risk of recurrence by some but not others. The decision of whether to undertake an anastomosis in the acute setting is dependent on a number of criteria: the frailty of the patient, the degree of contamination and sepsis, the preparedness of the bowel, and the experience of the surgeon. The Hartmann procedure entails resection of the sigmoid colon with formation of end colostomy and is the safest option when conditions do not favor primary anastomosis. Hartmann resections are not
without their own complications. Up to 50% of patients will never have their stoma closed, particularly the elderly.\textsuperscript{39,83,106,107} There is also definite morbidity (up to 16%) and mortality (up to 4%) related to restoration of continuity.\textsuperscript{36,94,106-109} Occasionally, there are complications related to rectal stump dehiscence.\textsuperscript{110}

Primary anastomosis can be performed in the emergency setting but only if conditions are wholly favorable.\textsuperscript{111,112} Performing anastomoses in the presence of gross purulent or fecal contamination is controversial and should only be performed by experienced hands. The requirement for bowel preparation for left-sided anastomosis is equally controversial, but recent studies have cast doubt on the need for this, albeit in the elective setting.\textsuperscript{113} Presacral drainage is often used at the end of the operation but without evidence of its effectiveness.\textsuperscript{114}

**ELECTIVE SURGERY**

Surgery should be reserved for patients who are medically fit with several proven attacks of acute diverticulitis or who have ongoing sequelae from complicated diverticular disease. In recent years, the role of surgery has been reassessed,\textsuperscript{115-118} and as a result, a more conservative approach has evolved, based on a better understanding of the natural history of diverticular disease, including that most patients will not get further episodes of acute diverticulitis and a significant minority of patients, whose principal symptom is chronic pain, will continue to be symptomatic after resection.\textsuperscript{119}

Elective resection has generally been offered to patients who have suffered 2 attacks of acute diverticulitis in a short period of time, but recommendations have ranged from 1 to 4 episodes.\textsuperscript{56,83,89} The argument has been that this will prevent recurrent diverticulitis as well as its associated complications.\textsuperscript{79,84,93,120-129} This is based on historical data that suggest recurrences of up to 67%, with higher morbidity (up to 60%) and mortality associated with recurrent diverticulitis particularly after two episodes.\textsuperscript{35,37,56,83,85-87,128,130-138} It was also previously demonstrated that patients older than 50 years respond less well to conservative treatment following successive attacks of diverticulitis; a response rate of only about 6% was reported for the third recurrence.\textsuperscript{136} In another series, rerecurrence was estimated at 2% per year with the first recurrence being the most
significant predictor of this. Most often, any recurrence that occurs does so in the first 6 months after the initial attack, and recent data would suggest that it is in fact failure of resolution of the inflammation from the first episode rather than a true recurrence. Some have argued that there is a reduction in the recurrence rate of diverticulitis from 12.5% to 6%, with good long-term results following surgery.

There is increasing evidence that conservative management is adequate in most patients following both complicated and uncomplicated attacks of diverticulitis in this situation. A large population-based study recently showed very few patients going on to have surgery after initial conservative treatment of diverticulitis. Another group showed that successful conservatively treated complicated disease, in particular abscesses, is not associated with further recurrence or complicated recurrences. A recent study followed 502 patients, 337 with uncomplicated diverticulitis and 165 with complicated diverticulitis, for a median of 101 months. Of the 320 patients with uncomplicated diverticulitis managed conservatively, 60 (18.8%) had one episode of recurrence, whereas 15 (4.7%) had 2 or more episodes. After an initial attack of uncomplicated diverticulitis, only 5.0% developed complicated disease. Complicated disease recurred in 24% of patients, compared with a recurrence rate of 23.4% in those with uncomplicated diverticulitis (P = .622). When recurrence occurred, it usually did so within 12 months of the initial episode.

Recent evidence suggests that less than a quarter of patients having emergency surgery for acute diverticulitis have a previous history, and often complications arise during the first attack of diverticulitis, rather than during subsequent episodes. Such episodes were associated with a more benign course and responded well to nonoperative management. Two groups have shown that the less severe and more readily conservatively managed complications of pericolic abscess occur in recurrent cases rather than free perforation. Following elective resection, up to 25% will continue to have symptoms suggesting a coexistent pathology such as irritable bowel. Up to 16% will develop recurrent diverticulitis, with a small percentage requiring further surgery. Furthermore, prophylactic colectomy has a mortality risk of up to 4%, and a diverting stoma is used in up to 14%, necessitating a further operation to reverse. Risk-reducing measures in elective surgery include weight control, routine
administration of prophylactic preoperative antibiotics, and preoperative optimization of the respiratory status of the patient with chronic pulmonary disease. Attempts have been made to stratify the management of diverticular disease by pathologic and radiologic means.\textsuperscript{148,149} In one study, patients characterized as having a mild attack of diverticulitis had a 14\% risk of having a recurrent episode, whereas severe forms had a risk of 39\%. Ultimately, the wide spectrum of disease encountered makes dogmatic statements about intervention unreliable, and sound clinical judgment is still required to decide when to intervene.

Indications for operative intervention are different in 2 patient subgroups: those younger than 50 years and the immunocompromised. Data on young patients with diverticular disease are mainly retrospective. The prevalence of colonic diverticula has been estimated at between 6\% and 9\% in the general population age 40 years or younger, with a male preponderance (62\%-100\%).\textsuperscript{123,150-152} Patients in this group are thought to have a more virulent course with more complicated recurrences, and an aggressive policy of surgical resection has been proposed,\textsuperscript{123,129,130,143,152-157} particularly in obese males.\textsuperscript{123,158,159} Others more recently have challenged this opinion, arguing that there is no difference between the young and old population.\textsuperscript{160} There were very few free perforations with recurrent attacks and certainly no increased mortality in this age group.\textsuperscript{78,87,132,151,157,161-164} Whether the higher propensity for a complicated course in this age group is a true association or the presentation has been altered because of delayed diagnosis remains debatable.\textsuperscript{147,165-167} Between 29\% and 55\% of younger patients will be readmitted to the hospital with acute diverticulitis following their initial presentation, with the majority (up to 88\%) of these subsequently undergoing elective or emergency surgery.\textsuperscript{82,143,152-154,168} A number of these patients were diagnosed at operation for another surgical condition, most often with appendicitis, and were thus often unnecessarily operated on.\textsuperscript{78,163,164} It is unclear whether there is an advantage to operating after the initial acute attack of diverticulitis in this age group, especially if it is uncomplicated.

It is uncertain whether patients who are chronically immunosuppressed are more at risk of developing diverticular disease. It is thought that patients who have long-term uremia have a higher incidence of diverticulosis, possibly due to chronic constipation and generalized tissue weakness. Patients with polycystic kidney disease have a very high incidence of colonic diverticular
Several groups have reported that immunocompromised patients with acute diverticulitis have a more complicated course compared to nonimmunosuppressed patients. Patients who are recipients of renal transplants have a high mortality rate from acute complicated diverticular disease. In some centers, routine colonic screening of patients awaiting renal allografts is performed.

There is limited evidence that the cessation of smoking and stopping NSAIDs will reduce the rate of recurrent attacks of diverticulitis. There is some evidence that the long-term administration of a poorly absorbed antibiotic will have such an effect. Mesalazine has been trialed both for treatment of acute attacks and prevention of recurrence, but there is insufficient evidence to support its use.

**ELECTIVE LAPAROSCOPIC SURGERY**

Laparoscopic colectomy has been practiced routinely for over 2 decades. Numerous randomized trials demonstrate laparoscopic surgery in colon cancer is oncologically equivalent to the open approach with better cosmesis, less analgesic usage, and shorter hospital stays. There is lower quality evidence for laparoscopic colectomy in diverticular disease, but results from specialized centers suggest good results. Some groups have included complicated cases, including abscesses and fistulas. Published studies comparing laparoscopic and open resection of left-sided colonic diverticular disease have demonstrated benefits in terms of shorter hospital stay and convalescence despite a longer operating time. Major complications and the length of the colon resection are generally the same when compared with the traditional open approaches. Conversions to open depend on factors such as the clinician’s surgical experience and the complexity of the diverticular complications involved.

Caution should be exercised because the laparoscopic approach in diverticular disease can be more technically challenging than operating on malignant disease because of the recurrent inflammation and fibrosis. Significant experience in laparoscopic surgery and appropriate patient selection are required to maintain the benefits of the laparoscopic approach with acceptably low morbidity rates.

Furthermore, publication bias is likely to promote laparoscopic resection
as being more favorable, and the true morbidity, cost, and conversion rates may differ from figures published in the medical literature. In over 1100 patients reported over the past 5 years, the postoperative complication rates range from 7.3% to 21%. Conversion rates range between 4% and 14%, operating time ranges from 141 to 300 minutes, and return of bowel activity takes between 2 and 2.9 days.185-187,189 A recent analysis of the cost of laparoscopic surgery compared with open surgery demonstrated that the total cost of the laparoscopic approach was significantly less (US$3458 vs US$4321; $P < .05).189 These economic factors will have ramifications for surgical treatment in the future.

Summary

The prevalence of diverticular disease has increased and is continuing to do so in Western countries. The management of diverticular disease is becoming an increasing financial burden to health systems with limited resources. There is little evidence that a change in lifestyle measures can reduce the prevalence of diverticular disease. Fortunately, colonic diverticula are usually asymptomatic.

The acute management of diverticulitis is usually conservative with antibiotics and bowel rest, with few patients needing emergency operations. Abscesses can be adequately treated with percutaneous drainage. When an operation is required, the quality of the surgery appears to be more important than whether the operation is undertaken open or laparoscopically. In the acute setting, the affected segment of colon should be resected. The place of elective resection is uncertain. The wide spectrum of disease encountered makes dogmatic statements about intervention unreliable, and sound clinical judgment is still required to decide when to intervene. Further prospective trials investigating recurrence rates, and in particular risk factors for recurrence, as well as the role of prophylactic surgery in the various subgroups are required.

**COLONIC VOLVULUS**

A colonic volvulus occurs when a segment of colon twists around its mesentery giving rise to a partial or complete bowel obstruction. This
condition is not just confined to humans with dogs and horses both suffering from this disease.

**Epidemiology**

Colonic volvulus occurs frequently in developing countries such as Africa and South America, accounting for at least 50% of causes of LBO, but in developed nations, it is third after cancer and diverticular disease, at about 10%.

In developed countries, sigmoid and cecal volvulus are the 2 most common forms of colonic volvulus, with the former increasing in incidence with age, especially in those older than 60 years. In sigmoid volvulus, there is a higher incidence in males due to their dolichomesocolic anatomy (sigmoid mesocolon is longer than wide) compared to females. In cecal volvulus, there is a younger age of presentation, usually around 40 years of age and particularly in women. Overall, the ratio of sigmoid to cecal volvulus is about 4:1. The other sites, including the descending colon, flexures, and transverse colon, are rarely involved. In developing countries, the peak incidence is in males in the 40- to 60-year age group, who account for up to 90% of cases.

**Etiology**

A redundant colon that is mobile on a long mesentery is a prerequisite that predisposes to colonic volvulus. Redundancy of the colon is due to colonic dysmotility, excessive fiber intake, or a genetic predisposition. Adynamic ileus and distal obstruction are also predisposing factors. In cecal volvulus, up to 50% will have a history of prior abdominal surgery. Volvulus in Western society is often seen in institutionalized, bed-bound elderly patients with an acquired megacolon. Mobility of the sigmoid colon is obvious with a long and narrow mesentery. In the right colon, poor fixation is often related to partial or complete malrotation of the bowel, and in the splenic flexure, volvulus occurs when there is congenital lack of fixation of the splenocolic, gastrocolic, and phrenocolic ligaments.
Morphologic Features

In colonic volvulus, there is axial twisting of the bowel loops around the vascular axis, leading to a closed-loop obstruction with bowel ischemia and potential gangrene. If neglected, perforation of this bowel loop may occur. In cecal volvulus, there is usually a counterclockwise axial twisting of the cecum, ascending colon, and terminal ileum around the mesenteric pedicle. Cecal bascule is a variant of the true cecal volvulus with the difference being an absence of the axial twist; rather, the redundant cecum folds back transversely and upward over the ascending colon. True cecal volvulus is about 9 times more common than cecal bascule. Bowel ischemia or infarction in this group can occur but is unusual. Ileosigmoid knotting occurs when the ileum gets caught up in the sigmoid volvulus and an ischemic process ensues in both the twisted bowel loops.

Presentation

Colonic volvulus commonly presents with bowel obstruction, vomiting, obstipation, abdominal pain, and distension. About half of patients will have symptoms suggestive of a previous attack. Clinical examination usually reveals a massively distended abdomen that is asymmetrical and tympanic. The rectum is invariably empty. Signs of peritonitis often indicate underlying complications of perforation or gangrene.

Complications

Perforation of the twisted segment of bowel (closed-loop obstruction) or bowel ischemia and infarction may occur. Secondary renal failure or multiorgan failure could arise because of third-space loss or loss from vomiting. Alternatively, this may be due to reperfusion injury after the volvulus is untwisted. Abdominal compartment syndrome is a rare complication.

Investigations

A plain supine abdominal x-ray is usually sufficient in the diagnosis of
sigmoid and cecal volvulus (Figs 43-10 and 43-11). Up to 40% cases of cecal volvulus are in fact misdiagnosed as sigmoid volvulus. In cecal volvulus, the dilated colon assumes the shape of a large coffee bean (“tear drop” or “comma” appearance) with 1 fluid level and the point directed toward the left upper quadrant (see Fig. 43-11). There is often a lack of gas in the distal colon, and up to half of patients will have dilated small bowel as well. In sigmoid volvulus, the shape is that of a “bent inner tube” with its point aimed at the right upper quadrant (see Fig. 43-10). Other features include “2 air to 1 fluid level” and a “pair of scales,” whereby the fluid levels are at different horizontal levels. Dilated proximal large bowel and small bowel may be evident. Rarely, even when present, is there free air under the hemidiaphragms due to the overwhelming amounts of colonic luminal gas that is present in the background. To confirm the diagnosis, a gastrografin (diatrizoate meglumine) or barium enema study may be performed to look for the “bird beak” sign that indicates the site of twisting of the colon. This, however, is becoming obsolete as CT scan is now readily available and commonly used to differentiate causes of abdominal pain. The “bird beak,” whirl, or coffee bean signs are the most diagnostic features of volvulus on CT scan (Figs 43-12 through 43-14). CT scans can also be used to help exclude other diagnoses, including causes of distal bowel obstruction that may be associated with the volvulus, as well as help determine if the volvulus is complicated by ischemia or perforation. Alternatively, a rigid or flexible sigmoidoscopy or colonoscopy can be performed. This has a higher rate of therapeutic success than an enema study, in particular for the sigmoid volvulus.
FIGURE 43-10  Plain supine abdominal x-ray of sigmoid volvulus (showing margins of volvulized sigmoid loop in a background of dilated proximal bowel).
FIGURE 43-11 Cecal volvulus with proximal small bowel obstruction.
FIGURE 43-12  Coronal CT scan section. Sigmoid volvulus with the “swirl sign.”
FIGURE 43-13  Axial CT scan section showing beaking at site of sigmoid volvulus.
Management

In Western countries, the mortality associated with colonic volvulus is high, at about 20% overall and even higher when there is concomitant gangrenous colon. This is primarily due to the high comorbidities of this particular group of patients.194

Management of colonic volvulus should include a combination of careful resuscitation, urgent diagnosis, and decompression as soon as feasible. Of note, reperfusion syndrome is a real phenomenon following de-torsion of an ischemic or gangrenous bowel segment. Potential serious bacterial/toxin translocation and multiorgan failure are consequences that the treating
Colonic volvulus especially involving the sigmoid colon may be decompressed by rigid sigmoidoscopy or colonoscopy. The latter has been shown to be more effective at decompression and carries a lower risk of complications. The twisting point is often found high above the anal verge with decompression manifesting as a sudden rush of flatus and liquid feces via the anus or sigmoidoscope. The mucosa of the obstructed loop and the site of twisting should be inspected to evaluate the level of bowel ischemia. If no immediate surgery is required, a rectal tube should be placed to prevent further recurrences of the volvulus to allow the continuing decompression of the obstructed colon. For recurrent sigmoid volvulus in a patient who may withstand surgery, a sigmoid colectomy with or without anastomosis, once the bowel is adequately decompressed, is warranted. In the absence of perforation, there is no difference in outcome between a primary anastomosis and Hartmann procedure for gangrenous disease. The mortality of this is only slightly higher at 5.5% (primary resection and anastomosis) versus 4.2% (Hartmann). The recurrence rate after resection is almost zero.

Laparotomy and de-torsion with or without colopexy is a poorer alternative with similar morbidity but higher recurrence of up to 40%. Similarly, there is a high recurrence rate for mesosigmoidoplasty. Surgery undertaken in these emergency situations had mortalities of 40% compared to 5.9% for elective operations. In patients who are medically at too high risk for an anesthetic, removing the rectal tube 48 hours later to allow the obstructed colon to deflate and then observing for 24 hours for recurrence before discharge is an option. Alternatively, colonoscopic-assisted placement of 2 colostomy tubes (percutaneous endoscopic colostomy) to fix the offending bowel loop to the anterior abdominal wall has recently been described in a series of 19 patients with good success and low morbidity.Only one patient had a recurrence requiring another tube colostomy to be inserted because of recurrence. Another patient died from tube dislodgement and peritonitis. Laparoscopic colopexy, extraperitonealization of the sigmoid colon, and laparoscopic colectomies have more recently been widely used. It should be noted that the redundant bowel can make laparoscopic retraction troublesome, and the redundancy in the bowel can facilitate colectomy through a relatively small incision without the need for laparoscopic assistance. A medial to lateral approach for laparoscopic-
assisted resection has been found to be advantageous. Cecal volvulus is more difficult to rectify using colonoscopy, primarily because of an inability to reach the obstructed right colon. There is also a higher risk of perforation. Consequently, surgery is often required. If feasible, an ileocolic resection with or without anastomosis is performed. This has the lowest recurrence rate but a high morbidity at about 30% and a mortality of up to 20%. Alternatively, cecopexy may be performed but is associated with a recurrence rate of approximately 20%. A tube cecostomy fixation (Fig. 43-15) has been advocated by some, claiming a low recurrence rate of about 2% and low morbidity, but others have shown that it has a morbidity of about 52% and mortality of 22%

![Cecal volvulus untwisted through lateral oblique incision and insertion of cecostomy tube (Foley catheter).](image)

**FIGURE 43-15** Cecal volvulus untwisted through lateral oblique incision and insertion of cecostomy tube (Foley catheter).

**Conclusion**

Colonic volvulus most commonly occurs in the sigmoid and is the third most common cause of bowel obstruction. It is readily seen on plain abdominal x-ray and CT scan. Sigmoid volvulus can often be nonoperatively
decompressed before a decision is made for definitive resection that rarely leads to recurrence. Cecal volvulus often requires an operation to fix it. Delayed management of volvulus may result in perforation, leading to high rates of complications and mortality, especially in this elderly age group.

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2002;89:546-554.


186. Reissfelder C, Buhr HJ, Ritz JP. Can laparoscopically assisted sigmoid resection provide


DEFINITION/INTRODUCTION

Colonic volvulus refers to the twisting of the colon around its mesenteric axis. Although an uncommon cause of large bowel obstruction in the United States, it is a potentially life-threatening condition that necessitates expedient surgical evaluation and treatment. The twisting of the colon results in a closed-loop obstruction, occlusion of the mesenteric vessels, and subsequent ischemia of the affected segment of bowel. Volvulus can affect any part of the bowel, and is classified based on the segment of colon involved. Given its redundancy and relatively long, narrowly-based mesentery, the sigmoid colon is the most common site of colonic volvulus, followed in frequency by the cecum. Other much rarer forms of colonic volvulus include cecal bascule, transverse colonic volvulus, ileosigmoid knotting, and splenic flexure volvulus. Sigmoid volvulus accounts for up to 80% of all colonic volvuli, while the cecum appears to be involved in approximately 20% of cases.\textsuperscript{1,2}

EPIDEMIOLOGY

In the United States, it is estimated that colonic volvulus accounts for less
than 5% of all large bowel obstructions (LBOs), making it the third most common cause of LBO after cancer and diverticular disease in adult patients.\textsuperscript{1–4} Interestingly, dramatic international geographic variation in the incidence of this disease process has been observed. In some countries, including Pakistan, India, and Brazil, sigmoid volvulus alone has been reported to account for 20% to 30% of all intestinal obstructions and is implicated in over 54% of obstructions in Ethiopia.\textsuperscript{1} It has long been known that colonic volvulus has a much higher incidence in parts of Africa, the Middle East, and South America. It has been postulated that this variability is related to the very-high-fiber diets common in these regions leading to colonic redundancy, as well as Chagas disease–related megacolon in South America.\textsuperscript{1}

Not only is there geographic variability in the incidence of colonic volvulus, but also in the demographics of the populations most commonly affected. In the United States and other Western developed nations, the stereotypical demographic of the patient presenting with sigmoid volvulus is an elderly, chronically ill, institutionalized patient with a history of chronic constipation. In addition, there seems to be an association with neuropsychiatric disorders such as Parkinson disease and dementia. However, these comorbidities do not necessarily correlate with volvulus in areas where colonic volvulus is a more endemic phenomenon.\textsuperscript{2}

While sigmoid volvulus occurs in similar proportions of men and women, with perhaps a slight male bias, cecal volvulus has a clear female predominance. Cecal volvulus also tends to affect younger patients, with a mean age of diagnosis around the fourth or fifth decade of life. Table 44-1 highlights some of the key differences between sigmoid and cecal volvulus.

### Table 44-1: Key Differences Between Sigmoid and Cecal Volvulus

\textsuperscript{a}
ETIOLOGY/PATHOPHYSIOLOGY

The pathophysiology of colonic volvulus is quite straightforward: the colon twists at least 180 degrees, resulting in closed-loop obstruction and occlusion of the vascular supply. Particularly in the case of sigmoid volvulus, the underlying mechanism of this twisting involves the presence of a large, floppy, redundant colon in combination with a long, narrow mesenteric base. This set of conditions, more common in elderly, infirm patients with constipation, accounts for the predominant involvement of the sigmoid colon. The relatively narrow mesentery provides a pivot point around which the heavy, mobile colon can rotate. In some cases, the colon may detorse spontaneously, and indeed, some patients report a history of similar symptoms at the time of presentation. However, the volvulus becomes problematic as it results in obstruction of the bowel lumen as well as occlusion of the arterial and venous blood supply, with a subsequent natural history of bowel gangrene, necrosis, and perforation.

Multiple underlying etiologies for this process have been proposed, all of which share the resulting pathogenesis of an enlarged, redundant colon that is prone to twisting. Chronic constipation and laxative use are likely the most common causes of sigmoid volvulus in the United States. However, a redundant colon can also contribute to the problem of constipation, making it difficult to ascertain the directionality of the causal relationship between these two processes. In other geographic areas, a high-fiber diet has been implicated, or possibly even genetic variation in colon and mesenteric length. In South America, Chagas disease is commonly an underlying cause of megacolon and subsequent volvulus. Hirschsprung disease is similarly associated with both a dilated colon and colonic volvulus.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Sigmoid Volvulus</th>
<th>Cecal Volvulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>60%-80% of colonic volvuli</td>
<td>~20% of colonic volvuli</td>
</tr>
<tr>
<td>Etiology/risk factors</td>
<td>Older, chronically ill, institutionalized; slight male predominance</td>
<td>Younger (40s-50s), female</td>
</tr>
<tr>
<td>Presentation</td>
<td>Chronic constipation</td>
<td>Congenital non-fixation of cecum</td>
</tr>
<tr>
<td>Imaging findings</td>
<td>Marked abdominal distention, consistent with LBO</td>
<td>Often less distention; consistent with distal SBO</td>
</tr>
<tr>
<td></td>
<td>“Coffee bean” or “bent inner tube” sign on KUB; cleft oriented toward L.I.Q</td>
<td>“Kidney bean” sign; cleft oriented toward RLQ</td>
</tr>
<tr>
<td>Success with endoscopic detorsion</td>
<td>Frequent</td>
<td>Rare to never</td>
</tr>
<tr>
<td>Definitive management</td>
<td>Sigmoidectomy</td>
<td>Right hemicolectomy</td>
</tr>
</tbody>
</table>

*While both involve twisting of a segment of the colon, these types of volvuli differ in important ways, suggesting that they may best be conceptualized as distinct disease processes.*
In contrast to sigmoid volvulus, in which the chronic colonic elongation that predisposes to twisting is generally conceptualized as an acquired condition, the pathogenesis of cecal volvulus may in fact be more congenital in nature. While the same underlying situation of a floppy colon is necessary for cecal volvulus, this is more commonly seen in the setting of either prior mobilization of the right colon or congenital non-fixation of the cecum. This notion is further suggested by the differences in patient demographics that have been observed between cecal and sigmoid volvulus. As noted earlier, cecal volvulus patients tend to be much younger, more often female, and of thinner body habitus. These characteristics as well as intraoperative findings suggest that incomplete congenital fixation of the cecum plays a primary role in the pathogenesis of cecal volvuli. Therefore, cecal and sigmoid volvulus should be thought of as distinct disease processes, affecting different patient populations and having different underlying etiologies.

**DIAGNOSIS**

Colonic volvulus can present as a partial or complete large bowel obstruction. Nonspecific signs and symptoms of acute bowel obstruction include nausea, vomiting, abdominal pain, distention, and constipation or obstipation. Sigmoid volvulus is often associated with significant abdominal distention, given the distal location of the obstruction, and obstipation. Cecal volvulus, in contrast, may present with less impressive distention and signs and symptoms consistent with distal small bowel obstruction. If the volvulus has progressed to gangrene and perforation of the involved colon, the patient may present with diffuse abdominal pain and tenderness consistent with peritonitis. Fever and leukocytosis are ominous signs suggestive of ongoing or impending bowel compromise.

The differential diagnosis for colonic volvulus includes other causes of mechanical and non-mechanical bowel obstruction, such as obstructing colon cancer, diverticular disease, and Ogilvie syndrome. These may be differentiated on the basis of acuity, associated signs and symptoms, and imaging. The patient may report a history of intermittent obstructive symptoms or chronic constipation, especially in the case of sigmoid volvulus.

The diagnosis of volvulus can often be made with plain radiographs alone. The classic “bent inner tube” or “coffee bean” sign on an anteroposterior
abdominal radiograph is diagnostic of sigmoid volvulus in up to 80% of cases. With this finding, the “coffee bean” arises from the pelvis, and the cleft is classically oriented toward the left lower quadrant, pointing in the direction of the sigmoid colon (Fig. 44-1). Additional findings suggestive of closed loop obstruction include air−fluid levels on supine or decubitus images and absence or paucity of gas in the rectum, which can be particularly helpful in differentiating this diagnosis from pseudo-obstruction. The diagnosis of sigmoid volvulus can be confirmed with a contrast enema demonstrating a bird’s beak appearance (Fig. 44-2). While this imaging study may also be therapeutic in some cases, resulting in colonic detorsion, contrast enema should be avoided if there is concern for perforation or bowel compromise.

FIGURE 44-1 “Coffee bean sign” of sigmoid volvulus. The convexity is located in the right upper quadrant, and the cleft points toward the left lower quadrant, where the sigmoid colon originates.
Contrast enema in the setting of sigmoid volvulus demonstrating bird’s beak appearance. The tapered appearance, or “bird’s beak,” of the contrast correlates with the twisted segment of colon.

The classic plain film finding of cecal volvulus is that of the “kidney bean,” in which the air-filled cecum is located in the left upper quadrant and the cleft points toward the right lower quadrant (Fig. 44-3). However, cecal volvulus can sometimes be more difficult to definitively diagnose with plain films alone, and therefore cross-sectional imaging can be useful. Markedly dilated cecum consistent with obstruction in association with mesenteric swirling is highly suggestive of volvulus. While sigmoid volvulus is associated with diffuse colonic dilation, given its distal location, the distal colon should be decompressed in the setting of cecal volvulus, and the small bowel may even not exhibit significant dilatation in the setting of a competent ileocecal valve.
FIGURE 44-3  “Kidney bean sign” of cecal volvulus. The convexity is located in the left upper quadrant, and the cleft points toward the right lower quadrant, where the cecum originates.

MANAGEMENT

The first consideration in the management of volvulus of any variety is resuscitation and correction of electrolyte abnormalities. The primary goals of surgical treatment for volvulus are to achieve emergent detorsion of the colon in order to restore blood supply and alleviate obstruction; to remove any gangrenous, necrotic, or perforated segments of bowel; and to reduce the risk of recurrent volvulus. In general, prompt treatment is necessary to avoid progression to necrosis and perforation. However, optimal operative timing and initial approach are dependent on patient condition and presentation.

Sigmoid Volvulus
In the absence of existing or threatened perforation, sigmoid volvulus can be managed initially with attempts at endoscopic detorsion. This procedure may be performed using either a colonoscope, sigmoidoscope, or most commonly, a rigid proctoscope. In the event of successful detorsion, which is accomplished in the majority of cases, placement of a rectal tube may facilitate ongoing decompression. Historically, reported risk of recurrent volvulus following endoscopic detorsion ranges from 23% to 71%, and therefore non-urgent or elective sigmoid colectomy is recommended after completion of resuscitation and bowel preparation. While sigmoidectomy is recommended for most of these patients, it is not mandatory, and should be considered in the context of the individual patient’s comorbidities, functional status, and life expectancy. In the elderly, poor surgical risk patient, prophylactic sigmoidectomy is often difficult for families and surgeons to strongly endorse after just the first bout of volvulus, and therefore it is more commonly performed only after recurrent episodes.

If, on the other hand, the patient exhibits signs concerning for gangrene, perforation, or peritonitis at the time of presentation, emergent surgical intervention is indicated, without an attempt at endoscopic decompression. In the absence of clear perforation, findings on endoscopic evaluation that suggest bowel compromise and warrant surgical exploration include mucosal necrosis, ulceration, or presence of dark blood. Depending on the degree of intraperitoneal contamination and the patient’s overall condition, surgical options include a Hartmann procedure versus sigmoid colectomy with primary anastomosis. The ability to perform a primary anastomosis is dependent on the quality of the proximal bowel as well as patient clinical condition in the operating room. While resection with primary anastomosis has clearly been demonstrated to be safe and effective in the semi-elective or elective treatment of sigmoid volvulus, the most commonly performed procedure in patients requiring emergent operation is a Hartmann procedure.

An alternative option to either endoscopic detorsion or sigmoid colon resection is operative detorsion with or without fixation of the colon. This approach should be utilized only when endoscopic decompression is not an option or fails to achieve detorsion, and when all bowel is viable. Fixation without resection, or sigmoidopexy, is typically reserved for patients deemed to be poor candidates for partial colectomy, and historically has been very
rarely used in patients with sigmoid volvulus. Figure 44-4 provides a basic algorithm outlining the typical approach and important considerations in the management of a patient with sigmoid volvulus.

**FIGURE 44-4** Basic algorithm for the management of a patient with sigmoid volvulus.

**Cecal Volvulus**

Unlike sigmoid volvulus, cecal volvulus can rarely be treated effectively endoscopically, and vascular compromise tends to occur earlier in the course of this disease. Because of these factors, early surgical intervention is usually indicated in patients with cecal volvulus. There are several operative options
in the acute treatment of cecal volvulus, including resection and primary anastomosis, resection with diversion, cecopexy, and cecostomy tube placement. Detorsion of the cecum with cecopexy is associated with recurrence rates up to 40%. Catheter tube cecostomy has been described for the treatment of cecal volvulus to achieve decompression, diversion, and cecal fixation. It has been advocated by some as a means to treat cecal volvulus while simultaneously avoiding resection of unprepped bowel. However, others have reported concerning complications with this technique, including cecal necrosis, intraperitoneal leakage, fistula, and recurrence rates up to 14%. Because of these limitations of non-resective operations in the treatment of cecal volvulus, and because these patients tend to be younger and healthier than their sigmoid volvuli counterparts, right colectomy has become the preferred surgical treatment for most patients with cecal volvulus. In addition, once the volvulized cecum is removed, there is often healthy-appearing terminal ileum and transverse colon with which a satisfactory primary anastomosis can be safely created. Thus, the preferred surgical treatment for acute cecal volvulus in most patients is a resection with primary anastomosis. Resection with ileostomy diversion may be indicated in a sicker patient or under the circumstances of significant intraabdominal sepsis. Cecostomy or cecopexy may be considered a last resort in the treatment of unstable patients otherwise unable to tolerate laparotomy and resection and in the absence of gangrene or necrosis.

Given the relative rarity of colonic volvulus, there has been a paucity of literature to guide the development of clear evidence-based practice guidelines. Halabi et al. recently performed a large retrospective review of administrative data in order to describe management trends of colonic volvulus in the United States from 2002 to 2010. This study, which used the National Inpatient Sample database, reported a nonoperative approach (enema or endoscopic decompression) used to manage 17% of cases. The majority of patients managed operatively underwent a resection (89% of surgical cases), while a minority underwent either detorsion without fixation (4.2%), fixation such as cecopexy or sigmoidopexy (3.3%), or enterostomy procedure such as cecostomy or sigmoidostomy (3.3%). Laparoscopy was used in less than 4% of patients overall undergoing surgery for colonic volvulus, but was found to increase in usage over the more recent years. The potential advantages of laparoscopy over a laparotomy for the treatment of volvulus are underwhelming. Because the pathophysiology of volvulus
requires a long colonic mesentery, most volvuli can be delivered and resected through a very small laparotomy incision, which is ultimately comparable in size to the extraction site incision required if performed laparoscopically. Furthermore, the long, redundant, acutely obstructed colon makes laparoscopic exploration technically quite difficult. For these reasons, authors have abandoned the laparoscopic approach in most cases of volvulus and believe the significant majority will continue to be done via a small laparotomy.

**PROGNOSIS**

The prognosis in patients suffering from colonic volvulus is clearly related to the severity of illness at the time of presentation. A recent large retrospective study of national administrative data in the United States sought to identify risk factors of mortality in patients undergoing surgery for sigmoid or cecal volvulus. This group reported an overall mortality of 9.4% and 6.7% in patients undergoing resection for sigmoid and cecal volvulus, respectively. The strongest predictors for mortality in those with sigmoid volvulus were presence of peritonitis, gangrene, or necrosis, stoma use, and coagulopathy. In patients presenting with cecal volvulus, coagulopathy, age >60 years, and metastatic cancer best predicted mortality following resection. Notably, in both groups, anastomotic complications occurred in over 15% of patients.

In a similar study using the California Inpatient Database, Kasten et al. reported a 21% mortality over 3 years in patients requiring total colectomy for the treatment of their volvulus. In contrast, patients treated with detorsion and fixation, but no bowel resection, had the lowest morbidity and mortality but were found to have a re-intervention rate of over 25% within an approximately 2-year follow up period. The significant mortality and morbidity associated with colonic volvulus is likely a reflection of both the severity of the disease process as well as the baseline comorbidity and poor functional status of patients that tend to be affected.

**OTHER FORMS OF VOLVULUS**

Cecal bascule is a variant of cecal volvulus in which the cecum folds anteriorly and superiorly on top of itself toward the fixed ascending colon,
creating an organoaxial rotation, rather than a true mesenteroaxial volvulus. This process occurs less frequently than true cecal volvulus, and is thought to be associated with less vascular compromise. In addition, cecal bascule may be more likely to spontaneously reduce, resulting in intermittent symptoms of cecal obstruction. Nonetheless, if unrecognized and persistent, cecal bascule can progress to ischemia, necrosis, perforation, and sepsis. Therefore, it is generally recommended to proceed with resective therapy for patients with acute, persistent cecal bascule, or those felt to have symptoms referable to intermittent, recurring cecal bascule.

Volvulus of the transverse colon has been described, but it occurs very infrequently. This process appears to be most similar to that of sigmoid volvulus, with chronic constipation acting as one of the major risk factors. Radiographically, it most closely resembles sigmoid volvulus, but can be differentiated by the more proximal site of obstruction demonstrated on contrast enema. As in the treatment of sigmoid volvulus, detorsion may be attempted in the appropriate setting via an endoscopic approach; however, there is a lower success rate, and the patient often ultimately requires surgical intervention.

Even less common than transverse colon volvulus is volvulus of the splenic flexure, which has been described in the literature as scattered case reports. Like sigmoid volvulus, chronic constipation is a common complaint among patients developing splenic flexure volvulus. The underlying pathophysiology of this condition appears to involve non-fixation of the splenic flexure, which may occur in the setting of prior mobilization of the splenic flexure or adhesion formation from prior abdominal surgery. Alternatively, it has been described in association with a congenital abnormality of the gastrocolic, splenocolic, or phrenocolic ligaments or lateral peritoneal attachments. Management of this problem is guided by the same principles used for sigmoid volvulus. Devitalized colon must be resected emergently, and partial colectomy should be considered to prevent recurrence.

Finally, a type of volvulus termed the ileal-sigmoid knot is a relatively well-described entity in regions where colonic volvulus is more common. Also known as “compound volvulus” or “double volvulus,” this condition is a variant of sigmoid volvulus. As its name implies, ileal-sigmoid knotting occurs when the ileum wraps around the base of the sigmoid colon, resulting
in two closed-loop obstructions. It occurs predominantly in men and has a mean age of diagnosis around 40 years. This form of volvulus is associated with more profound and early malperfusion of the bowel. Importantly, endoscopic detorsion is often futile in the setting of ileosigmoid knotting, and therefore it is crucial to differentiate this process from isolated sigmoid volvulus. Emergent laparotomy should not be delayed. It is recommended that sigmoid resection be performed regardless of bowel viability, and that the decision to resect the involved portion of ileum be guided primarily by evidence of gangrene.

**SPECIAL POPULATIONS**

There are several unique populations of patients worth noting in relation to colonic volvulus. Sigmoid volvulus is reportedly one of the most common, albeit still rare, causes of large bowel obstruction in pregnant women. It is hypothesized that the gravid uterus displaces the sigmoid colon out of the pelvis and thereby predisposes it to twisting at its point of mesenteric fixation. This complication of pregnancy occurs most frequently in multiparous women, and during the third trimester. It can be diagnosed using MRI in non-emergent settings in order to avoid ionizing radiation exposure to the fetus. If possible, endoscopic detorsion is favored over operative treatment in these patients. Regardless, rates of maternal and fetal mortality associated with the diagnosis of sigmoid volvulus are reportedly as high as 14% and 28%, respectively.

Although rare, colonic volvulus has also been reported in children. It seems to occur most commonly in males and has an association with Hirschsprung disease. Indeed, nearly 20% of children presenting with sigmoid volvulus are found to have comorbid Hirschsprung disease, which likely increases one’s risk of volvulus due to chronic constipation and bowel distention. Mortality is significant in this population, with reported rates ranging from 11% to 22%.

**CONCLUSIONS**

Colonic volvulus is a rare but potentially life-threatening cause of large
bowel obstruction. It most commonly involves either the sigmoid colon or the cecum, and results in obstruction and strangulation, which can progress to gangrene and perforation. Sigmoid volvulus occurs in the setting of a large redundant colon in combination with a long, narrow mesentery, which is often the result of longstanding chronic constipation, while cecal volvulus is associated with congenital non-fixation of the cecum. Sigmoid volvulus can often be managed initially with endoscopic detorsion, followed semi-electively by sigmoid resection, while the management of cecal volvulus almost universally requires early cecal resection.

REFERENCES


**CROHN’S DISEASE**

*Heather Yeo • Alessandro Fichera • Roger D. Hurst • Fabrizio Michelassi*

*Crohn’s disease* is a chronic inflammatory condition of the gastrointestinal (GI) tract that can give rise to strictures, inflammatory masses, fistulas, abscesses, hemorrhage, and cancer. This disease commonly affects the small bowel, colon, rectum, or anus. Less commonly, it can also involve the stomach, esophagus, and mouth. Often, the disease will simultaneously affect multiple areas of the GI tract.

The etiology of Crohn’s disease is not known and there is no curative treatment. Current medical and surgical treatment is effective at controlling the disease, but even with optimal treatment, recurrences and relapses are frequent. The combined approach of optimal medical treatment with timely and strategic surgical intervention offers the most effective management to patients affected by Crohn’s disease. Care of patients with Crohn’s disease, however, can be particularly challenging, as it has a myriad of manifestations and potential complications. Additionally, its course and response to therapy can be difficult to predict. To add to the overall complexity, there are many therapeutic options that must be tailored to each individual patient and to each site of involvement to achieve optimal outcomes.


**HISTORY**

Crohn’s disease became recognized as a specific pathologic entity in 1932 when Crohn and colleagues first identified regional enteritis as a unique clinical entity.\(^1\) In retrospect, case descriptions of what appeared to be Crohn’s disease date back to at least 1612, when Fabry reported on the death of a boy experiencing severe abdominal pain.\(^2\) Autopsy revealed a contracted ulcerated cecum and ileum with complete bowel obstruction. In 1761, Morgagni described a case of an inflamed ileum with perforation and thickened mesentery in a young man with a history of diarrhea and fever.\(^3,4\)

It is unclear how common Crohn’s disease might have been before 1932, as it is likely that cases of this disease occurring in an era of limited abdominal surgery may have been mistaken for other processes such as tumor or intestinal tuberculosis. In 1913, Sir Dalziel of Glasgow, Scotland, reported in the *British Medical Journal* on 13 patients and provided what is now recognized as a classic clinical and pathologic description of Crohn’s disease.\(^5\) Although not often cited, Dalziel’s description predates the one by Crohn and colleagues, and some have argued that the disease should be known by the eponym “Dalziel-Crohn disease.”

After the report by Crohn and colleagues, increased awareness of the disease led to a marked increase in reported cases in the 1930s through the 1950s. The general public’s awareness of the disease increased when, in 1956, one of the most famous figures of the 20th century, President Dwight Eisenhower, was diagnosed with Crohn’s disease of his terminal ileum. That same year, President Eisenhower underwent intestinal bypass surgery with the small intestine proximal to the area of disease anastomosed to the transverse colon.\(^6\) Following this operation, he remained relatively free of symptoms for the remainder of his life.\(^7\)

Early in the history of Crohn’s disease, optimal surgical management remained disputed. Initially, many thought that the disease was one of both the bowel and the mesentery, and similar to malignancies, wide excision with radical dissection of the mesentery was believed to be the best way to provide for the optimal long-term outcome.\(^8\) It was also appreciated that diversion of the fecal stream was effective at decreasing active inflammation and ameliorating symptoms. Frequently performed in the 1940s and 1950s, bypass operations are now only rarely undertaken for Crohn’s disease, given
the risk of malignancy in the excluded segment.\textsuperscript{9-11} Additionally, a greater understanding of the clinical course of Crohn’s disease has led to more conservative resections, as it is appreciated that wide surgical margins of normal tissue and radical resection of the mesentery do not affect early recurrence of disease.

Despite the increased attention given to Crohn’s disease of the small intestine, Crohn’s colitis was not widely recognized as a form of Crohn’s disease until 1960 when Lockhart-Mummery and Morson firmly established the pathologic criteria for distinguishing Crohn’s disease from idiopathic ulcerative colitis.\textsuperscript{12}

**EPIDEMIOLOGY**

Since the original description of Crohn’s disease in 1932, the number of reported cases has increased greatly. Today, it is estimated that the incidence of Crohn’s disease in the United States is approximately 4 new cases per year for every 100,000 persons. Because this disease is chronic and patients live for many years with the ailment, the prevalence is much higher and is reported to be between 80 and 150 cases per 100,000 persons.\textsuperscript{13,14} The incidence of Crohn’s disease increased rapidly from 1930 to at least the 1980s, but more recently, the incidence of new cases now appears to have stabilized.

The United States, Canada, and Europe have the highest incidence of Crohn’s disease. It is much less common in Asia, South America, and Japan. Crohn’s disease is believed to be uncommon in Africa, but accurate data regarding the incidence of inflammatory bowel disease in this region of the world are lacking. The peak age of presentation for Crohn’s disease is between 15 and 25 years old. As such, Crohn’s disease typically affects young adults, yet the disease can occur at almost any age. It should be noted, however, that Crohn’s disease is very rare in children younger than 6 years.\textsuperscript{15}

In the United States, the incidence of Crohn’s disease is highest among Caucasians, low among blacks, and lowest among Hispanics and Asians. It is 3 to 4 times more common among ethnic Jews than non-Jewish whites. It also appears to be slightly more common in women than in men, although a slight male predominance has been reported in some populations.\textsuperscript{16}

Familial clusters of Crohn’s disease are not uncommon, with a 6- to 10-
fold increase in the risk of this disease in first-degree relatives of those affected by this disease or its sister ailment, ulcerative colitis. Although familial aggregations are common, the distribution within families does not indicate a pattern of simple Mendelian inheritance.

**ETIOLOGY**

The etiology of Crohn’s disease is not known. Many possible causes have been the subject of both speculation and investigation. Basic science research into the molecular biology of Crohn’s disease has begun to give some better insight into the genetics of this condition, but much regarding its ultimate causes remains unclear.

It is known that Crohn’s disease is an altered immune response that results in inflammation and destruction of intestinal tissues. It is not clear if this altered immune response is the result of a primary dysfunction in the gut-related immune system or whether an unknown pathologic trigger induces an otherwise normal immune system to overreact. Most believe that Crohn’s disease occurs in individuals with a genetic predisposition and that development of the disease is dependent on exposure to environmental triggers that start the pathologic sequence that ultimately manifests as Crohn’s disease.

To date, no specific primary defect in the systemic or mucosal immune system has been identified. Studies of intestinal transport mechanisms have demonstrated an increase in intestinal permeability in both Crohn’s disease patients and their symptom-free first-degree relatives. This has led some to speculate that Crohn’s disease is the result of an altered mucosal barrier function that allows abnormal interactions to take place between the multitude of antigenic substrates normally found in the gut lumen and the immunocompetent tissue of the submucosa.

As indicated by the observed familial aggregations and variability of risks among differing ethnic and racial groups, a genetic predisposition is likely to have a major role in the etiology of Crohn’s disease. The distribution of Crohn’s disease within family aggregates is complex and defies classification with simple Mendelian transmission of disease. Genetic linkage studies have identified susceptibility to Crohn’s disease to the *CARD15/NOD2* gene mapped to chromosome 16q12. CARD15 is a gene product related to...
innate immunity, and it is preferentially expressed to Paneth’s cells of the ileum.\textsuperscript{24,25} While the *CARD15/NOD2* gene has been linked to susceptibility to Crohn’s disease, the known mutations of *CARD15* are neither necessary nor sufficient to contract this disease. Hence, it appears that the genetic relationship of *CARD15/NOD2* to Crohn’s disease is complex and still poorly understood.

The suspicion that infectious agents may play a role, either directly as a primary cause of Crohn’s disease or indirectly as a trigger to stimulate a defective immune system, has generated much attention. This hypothesis has always found strength in the identification of noncaseating granulomas as the characteristic histopathologic lesion found in Crohn’s specimens and in the isolation of *Mycobacterium paratuberculosis* from resected Crohn’s disease specimens. This finding has been far from consistent, and even sensitive polymerase chain reaction studies have been unable to provide definitive evidence for the presence of *M paratuberculosis*–specific DNA in Crohn’s disease–affected segments of the bowel. Other infectious agents have been studied and shown not to be causative agents for Crohn’s disease. These include measles virus, non-pylori *Helicobacter* species, *Pseudomonas*, and *Listeria monocytogenes*.\textsuperscript{26} To date, no single infectious agent has been consistently associated with Crohn’s disease.

Although diet modification can ameliorate the symptoms of Crohn’s disease, no dietary factor has been identified as its cause. Smoking, however, has been associated with the development of Crohn’s disease, with smokers having a substantially higher risk for contracting this disease than nonsmokers.\textsuperscript{27-30} Additionally, smoking is known to exacerbate existing Crohn’s disease and can accelerate its recurrence after resection.\textsuperscript{31,32} The component of cigarette smoke that is responsible for these deleterious effects on the clinical course of Crohn’s disease is not known.

**PATHOLOGY**

The earliest gross manifestations of Crohn’s disease are the development of small mucosal ulcerations called aphthous ulcers.\textsuperscript{33} Aphthous ulcers appear as red spots or focal mucosal depressions and typically occur directly over submucosal lymphoid aggregates. As the inflammation progresses, the ulcers enlarge and become stellate. The enlarging ulcerations then coalesce to form
longitudinal mucosal ulcerations. In Crohn’s disease of the small bowel, these linear ulcerations almost always occur along the mesenteric aspect of the bowel lumen. Further progression leads to a serpiginous network of linear ulcerations that surround islands of edematous mucosa producing the classic “cobblestone” appearance. Mucosal ulcerations may penetrate through the submucosa to form intramural channels that can bore deeply into the bowel wall and create sinuses, abscesses, or fistulas.

The inflammation process progresses to extend through all layers of the bowel wall. The inflammation of Crohn’s disease also involves the mesentery and regional lymph nodes such that the mesentery may become massively thickened. With early acute intestinal inflammation, the bowel wall is hyperemic and boggy. As the inflammation becomes chronic, fibrotic scarring develops and the bowel wall becomes thickened and leathery in texture.

Histopathologic examination of Crohn’s disease typically demonstrates transmural inflammation characterized by multiple lymphoid aggregates in a thickened submucosa. Lymphoid aggregates may extend beyond the mucosa and can be found within the muscularis propria. The presence of well-formed lymphoid aggregates in an edematous fibrotic submucosa is a classic histologic feature of the disease. Another sentinel microscopic feature of Crohn’s disease is the presence of noncaseating granulomas. Noncaseating granulomas are a valuable diagnostic feature of Crohn’s disease, but they are seen in only 50% of resected specimens and are rarely seen on endoscopic biopsies. Additionally, the presence of granulomas does not correlate with disease activity, as areas of active inflammation are no more likely to contain granulomas than areas of quiescent disease.

CLINICAL PRESENTATION

The clinical presentation and symptoms of Crohn’s disease vary greatly depending on the segment of intestine involved and the predominant features of the disease: stricturing, perforating, or inflammatory. While the next few paragraphs discuss the influence of disease patterns and locations, there are additional more complex classifications that are used to subcategorize disease. The most common of these are the Rome, Montreal, and Vienna classifications (Table 45-1). These classifications are used help to
guide clinical decisions and frame medical and surgical management.\textsuperscript{36,37}

### TABLE 45-1: COMPARISON OF ROME, VIENNA, AND MONTREAL CLASSIFICATION SYSTEMS FOR CROHN’S DISEASE

<table>
<thead>
<tr>
<th>Rome Classification</th>
<th>Vienna Classification</th>
<th>Montreal Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td>A1 &lt;40</td>
<td>A1 ≤16</td>
</tr>
<tr>
<td>A2 ≥40</td>
<td>A2 17-40</td>
<td></td>
</tr>
<tr>
<td>A3 &gt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease location</td>
<td>Stomach/duodenum</td>
<td>L1 terminal ileal</td>
</tr>
<tr>
<td>Jejunum</td>
<td>L2 colonic</td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>L3 ileocolonic</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>L4 upper GI</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>L4 isolated upper GI modifier (added to L1-L3 when concomitant upper GI disease present)</td>
<td></td>
</tr>
<tr>
<td>Anal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease extent</td>
<td>Localized</td>
<td>B1 nonstricturing, nonpenetrating</td>
</tr>
<tr>
<td>Diffuse</td>
<td>B1 nonstricturing, nonpenetrating</td>
<td></td>
</tr>
<tr>
<td>Disease behavior</td>
<td>Inflammatory</td>
<td>B2 stricturing</td>
</tr>
<tr>
<td>Fistulizing</td>
<td>B2 stricturing</td>
<td></td>
</tr>
<tr>
<td>Fibrostenoic</td>
<td>B3 penetrating</td>
<td></td>
</tr>
<tr>
<td>Operative history</td>
<td>Primary</td>
<td>B3 (internal) penetrating</td>
</tr>
<tr>
<td>Recurrent</td>
<td>p = perianal disease modifier (added to B1-B3 when concomitant perianal disease present)</td>
<td></td>
</tr>
</tbody>
</table>


### Patterns of Disease

Crohn’s disease can be categorized into 3 general manifestations: stricturing disease, perforating disease, and inflammatory disease.\textsuperscript{38} These 3 classes do not represent truly distinct forms of the disease; rather, they are terms that are used to describe the predominant gross manifestation of the disease.\textsuperscript{39} It is typical for more than 1 pattern to occur in the same patient or even the same segment of intestine; even so, 1 pattern tends to predominate in most cases. It is generally the predominant pattern of disease that determines the clinical presentation and affects the therapeutic options.

### STRICTURING PATTERN

Chronic inflammation of Crohn’s disease results in the development of fibrotic scar tissue that constricts the intestinal lumen with cicatricial
strictures, often referred to as “fibrostenotic lesions.” Patients with a stricturing pattern of this disease generally develop partial or complete intestinal obstruction, and hence their symptoms are primarily obstructive in nature. Being the result of submucosal deposition of connective tissue, fibrostenotic strictures are not reversible with medical therapy. Once fibrostenotic areas become symptomatic, significant improvement rarely occurs and surgical intervention is often required. While surgery is clearly the standard of care for these patients, there are data on successful treatment with endoscopic balloon dilation and stenting in selected patients with strictures refractory to medical therapy.

PERFORATING PATTERN

Perforating Crohn’s disease is characterized by the development of sinus tracts, fistulas, and abscesses. Penetrating sinus tracts develop from deep mucosal ulcerations. These sinus tracts penetrate through the muscularis propria and give rise to abscesses or to fistulas if they penetrate into surrounding structures. The term “perforating” disease can be misleading, as free perforation with spillage of intestinal contents into the abdominal cavity is not a common phenomenon with Crohn’s disease. Inflammatory response around the advancing sinus tract typically results in adhesion to surrounding structures. The sinus usually bores through the area of adhesion such that abscess formation or fistulization to other structures occurs much more often than free perforation into the abdominal cavity. Typically, perforating disease is accompanied by a degree of stricture formation, but the fistula or abscess generated by the perforating component of the disease dominates the clinical picture.

INFLAMMATORY PATTERN

The inflammatory pattern of Crohn’s disease is characterized by mucosal ulceration and bowel wall thickening. The edema that results from inflammation can lead to an adynamic segment of intestine and luminal narrowing. This pattern often gives rise to obstructive symptoms in the small intestine and diarrhea in the colon. Of the 3 patterns of Crohn’s disease, the inflammatory pattern is much more likely to respond to medical therapy.
Location of Disease

Crohn’s disease is a panintestinal condition that may affect any area from the mouth to the anus. The most commonly affected location is the terminal ileum, and one-fifth of all patients have more than 1 intestinal segment affected simultaneously.

CROHN’S DISEASE OF THE FOREGUT

Crohn’s disease of the upper GI tract gives rise to symptoms of nausea, vomiting, dysphagia, or odynophagia. Oral Crohn’s disease usually manifests with aphthous ulcers in the hard palate that may cause discomfort, especially during mastication and deglutition. Esophageal Crohn’s disease is uncommon, but it is believed to be more frequent in children than in adults. Esophageal involvement in Crohn’s disease may be asymptomatic or may give rise to dysphagia or odynophagia. Esophageal Crohn’s disease is associated with Crohn’s disease elsewhere within the GI tract, as disease isolated to the esophagus is extremely rare. Symptomatic Crohn’s disease of the stomach and duodenum is more common than disease of the esophagus, yet both locations are the least frequently involved by Crohn’s disease. The symptoms are usually related to the obstructive nature of the disease with delayed gastric emptying, a sense of postprandial gastric fullness, nausea, and vomiting.

CROHN’S DISEASE OF THE SMALL INTESTINE

Abdominal pain is the predominant symptom of small bowel Crohn’s disease, as it occurs in 90% of cases. Abdominal pain may be the result of obstructive or septic complications. Pain related to partial obstruction is mostly postprandial and crampy in nature; pain from septic complications is typically steady and associated with fevers. Other common symptoms and findings include anorexia and weight loss. Weight loss is usually related to food avoidance, but in severe cases, it may be the result of malabsorption. With disease of the small intestine, patients may develop a palpable mass, usually located in the right lower quadrant, related to an abscess or phlegmon in perforating disease or a thickened loop of intestine in obstructive disease. Evidence of fistulization to the skin, urinary bladder, or vagina may also be
elicited with an accurate history and physical examination.

**CROHN’S COLITIS**

Crohn’s involvement of the colon typically results in diarrhea that may or may not be bloody. Acute flares of Crohn’s colitis are often associated with fever and abdominal pain that is often exacerbated by bowel movements. Strictures of the colon with more advanced disease can give rise to colonic obstruction. Like Crohn’s disease of the small intestine, Crohn’s colitis can give rise to abscess formation and fistulas. Toxic megacolon can occur with Crohn’s disease, but this severe complication is rare and less frequently seen than in ulcerative colitis.\(^{43}\)

**PERINEAL CROHN’S DISEASE**

Crohn’s disease frequently affects the anal crypts and gives rise to perianal fistulas, abscesses, and anal strictures. Perineal Crohn’s disease is also associated with hypertrophic perianal skin tags, fissures, and perineal scarring. Approximately 40% of patients with Crohn’s will develop perineal manifestations.\(^{44,45}\) Anal Crohn’s disease is almost always associated with Crohn’s disease present elsewhere in the GI tract, although perianal disease can be the initial symptomatic manifestation of Crohn’s disease.

**EXTRAINTESTINAL CROHN’S DISEASE**

In addition to the inflammation of the GI tract, a variety of extraintestinal manifestations can occur in Crohn’s disease. These include ocular, dermatologic, hepatobiliary, and joint disorders.\(^{46,47}\) Such extraintestinal manifestations occur in a minority of patients, but, when present, they produce symptoms that can be more severe than those of the primary intestinal disease. Ocular manifestations of Crohn’s disease include uveitis and episcleritis.\(^{48}\) Cutaneous manifestations of Crohn’s disease include erythema nodosum and pyoderma gangrenosum. Joint disorders such as ankylosing spondylitis, sacroiliitis, and seronegative polyarteritis can occur. Patients with Crohn’s disease are also at risk for the development of primary sclerosing cholangitis. However, the risk for primary sclerosing cholangitis is much less in Crohn’s disease patients than in patients who suffer from
Peripheral polyarteritis, episcleritis, uveitis, and erythema nodosum typically correlate with the activity of intestinal Crohn’s disease. These particular extraintestinal manifestations usually regress with complete surgical resection of the affected segment of intestine or with successful medical control of the intestinal inflammation. Pyoderma gangrenosum may also improve with treatment of primary intestinal disease, but available clinical data on this particular issue have not always been consistent. The clinical course of ankylosing spondylitis and primary sclerosing cholangitis tends to be independent of the level of disease activity within the intestine. Ankylosing spondylitis and primary sclerosing cholangitis do not improve with surgical resection of the Crohn’s disease–affected bowel.

**DIAGNOSIS**

The onset of Crohn’s disease is often insidious, and many patients will experience some symptoms for months or even years before the diagnosis is made. The diagnosis of Crohn’s disease is typically made by a thorough history and physical examination along with intestinal radiography, endoscopy, and pathologic confirmation. There is no specific laboratory test that is diagnostic for Crohn’s disease, although serologic and inflammatory markers are typically elevated and correlate with disease activity (eg, calprotectin and C-reactive protein). Advanced imaging studies such as computed tomography (CT) scan or magnetic resonance imaging (MRI) can assess or detect some of the complications and manifestations of Crohn’s disease but do not replace endoscopic and pathologic confirmation.

**History and Physical Examination**

The symptoms of Crohn’s disease are dependent on the location of the involved segment, the pattern and the severity of disease, and the associated complications. As noted previously, in most cases, the onset of disease is gradual, with the most common complaints being intermittent abdominal pain, bloating, diarrhea, nausea, vomiting, weight loss, and fever. Patients may also have symptoms related to complications of the disease, including abdominal masses, pneumaturia, perianal pain and swelling, or skin rash. In
some cases, the onset of symptoms can be more sudden, with patients relating a history reminiscent of acute appendicitis. In these cases, pain in the right lower quadrant may have been present only for a few hours or days. However, a brief history of symptoms such as these is atypical.

In patients suspected of having Crohn’s disease, a complete physical examination should include a thorough abdominal assessment and digital rectal exam. In cases of ileal Crohn’s disease, tenderness is typically present in the right lower quadrant, and occasionally a palpable mass is present. The oral cavity should be examined for the presence of aphthous ulcers. The perianal area should be examined for the presence of fistulas, abscesses, or enlarged skin tags. A digital rectal examination should assess for the presence of anal strictures, fissures, and rectal mucosal ulcerations. The skin in the extremities should be examined for erythema nodosum and pyoderma gangrenosum.

**Imaging**

**SMALL BOWEL RADIOGRAPHY**

Upper intestinal contrast studies, either small bowel follow-through or enteroclysis, are the best means for assessing the small bowel for Crohn’s disease. The radiographic abnormalities of small bowel Crohn’s disease are often distinctive (Fig. 45-1). With early Crohn’s disease, mucosal granulations with ulceration and nodularity can be identified. Thickening of the mucosal folds and edema of the bowel wall itself can be demonstrated as the disease progresses. With more advanced disease, cobble stoning becomes radiographically apparent. Small bowel contrast studies can also provide information regarding enlargement of the mesentery, as well as formation of an inflammatory mass or abscess. Such findings are demonstrated by a general mass effect separating and displacing contrast-filled loops of small intestine (see Fig. 45-1; Fig. 45-2). Small bowel contrast studies can demonstrate some of the complications of Crohn’s disease, including high-grade strictures and fistulas. It is important to note, however, that small bowel radiography may not identify all such lesions. For instance, many enteric fistulas including ileosigmoid and ileovesical fistulas are not typically demonstrated on contrast radiography. Thus, the absence of radiographic evidence for fistulization does not exclude this possibility. Additionally,
small bowel studies may not demonstrate all the areas of disease with significant strictures.\textsuperscript{59} While small bowel radiographs may underestimate the extent of complicated Crohn’s disease, small bowel studies performed by an experienced GI radiologist are very effective as a diagnostic tool for this disease. Besides their diagnostic utility, small bowel radiographs can also help in assessing the extent of the disease by identifying the location and length of involved and uninvolved intestine and by recognizing whether the disease is continuous or discontinuous with skip lesions separated by areas of normal intestine (Fig. 45-3). Experienced radiologists can also assess areas of luminal narrowing and determine if they are the result of acute inflammatory swelling or are the result of fibrostenotic scar tissue. Such a distinction provides valuable information regarding the value of medical therapy versus early surgical intervention, as inflammatory stenoses are likely to respond to medical therapy whereas fibrotic strictures are best treated with surgery.
FIGURE 45-1 Small bowel radiograph demonstrating Crohn’s disease of the terminal ileum. (Reproduced with permission from the University of Chicago General Surgery Archives.)
FIGURE 45-2  Small bowel radiograph demonstrating Crohn’s disease of the terminal ileum with high-grade strictures and ulcerations. (Reproduced with permission from the University of Chicago General Surgery Archives.)
FIGURE 45-3  Small bowel radiograph demonstrating Crohn’s disease with strictures in the jejunum. (Reproduced with permission from the University of Chicago General Surgery Archives.)

ENDOSCOPY

Upper and lower endoscopies allow for inspection of mucosal disease and provide an opportunity for a biopsy for histologic evaluation. Upper endoscopy is useful in the diagnosis of mucosal lesions of the esophagus, stomach, and duodenum; it also easily identifies strictures and grades their severity. Characteristic colonoscopic features of Crohn’s disease include aphthous ulcers, longitudinal ulcerations, skip lesions often with rectal sparing, pseudopolyps, and strictures. In many cases, the terminal ileum can be entered and evaluated.
CAPSULE ENDOSCOPY

Capsule endoscopy is a new tool in the diagnosis and evaluation of Crohn’s disease. With this study, a small camera embedded within a capsule-size casing is swallowed, and images from the camera are transmitted to a small electronic receiver worn by the patient. Images from the capsule endoscopy can detect subtle mucosal lesions that may not be apparent on small bowel x-rays. Prior to the capsule endoscopy, patients with suspected Crohn’s disease should undergo a small bowel contrast study to exclude stricture formation, as the capsule may fail to pass through areas of narrowing and result in intestinal obstruction. The value of capsule endoscopy in the diagnosis of Crohn’s disease has been recently evaluated in a prospective study from the Mayo Clinic. This study compared capsule endoscopy, CT enterography (CTE), ileocolonoscopy, and small bowel follow-through in the diagnosis of small bowel Crohn’s disease in a prospective blinded trial and found that the sensitivity of capsule endoscopy was not significantly different from that of the other tests. A meta-analysis of capsule endoscopy studies comparing it to CTE suggested that the prevalence of abnormalities detected on capsule endoscopy was 38% higher than that of CTE. However, this value was significantly higher than CTE only for the subgroup of patients with known Crohn’s disease. The need for a preliminary small bowel contrast study to detect asymptomatic partial small bowel obstruction before the capsule endoscopy can be safely performed and the lack of a clear advantage over other imaging studies limit the utility of capsule endoscopy as a first-line test in Crohn’s disease and perhaps reserves this study for those cases in which there is a substantial diagnostic uncertainty.

COMPUTED TOMOGRAPHY

CT findings of uncomplicated Crohn’s disease are nonspecific, and routine CT is not necessary for the diagnosis of Crohn’s disease. CT, however, is very useful in identifying enteric involvement (>90%) and complications associated with Crohn’s disease. Specifically, CT can readily identify thickened and dilated intestinal loops, inflammatory masses, abscesses, and hydronephrosis resulting from retroperitoneal fibrosis and ureteral narrowing. CT scans may also raise suspicion for an enterovesical fistula as suggested by the presence of air within the urinary bladder. More recently, cross-sectional
imaging techniques have assumed an increasing role in the imaging of patients with Crohn’s disease. Using ileoscopy and biopsy of the terminal ileum as reference to evaluate the performance characteristics of cross-sectional enterography, CTE has been shown to have a higher sensitivity than barium small bowel follow-through. These findings have convinced many to use CTE combined with ileocolonoscopy as a first-line test for the diagnosis and staging of Crohn’s disease. CTE exploits the high spatial resolution and speed of modern CT, using large volumes of neutral oral contrast agents to generate detailed images of the small bowel wall, lumen, and mesentery. In addition, CTE has several potential advantages over barium studies in the identification of fistulizing disease. Unlike traditional fistulography, CTE does not suffer from superimposition of bowel loops and displays the mesentery, retroperitoneal, and abdominal wall musculature, typically involved by fistulas. Sinus tracts and abscesses can also be readily characterized by CTE. Widespread access and rapid scan time make CT useful and convenient; however, recent concerns about radiation-induced cancer arising from medically related CT have stimulated a reassessment of the role of CTE in young Crohn’s disease patients and have prompted many to encourage the use of magnetic resonance enterography (MRE).

MAGNETIC RESONANCE ENTEROGRAPHY

MRE has similar advantages to CTE, such as the ability to evaluate the entire small bowel, detect transmural inflammation, grade the severity of inflammation, and detect extracolonic inflammation, without the requirement of ionizing radiation. In fact, in a recent study, MRE was shown to have almost identical sensitivities to CTE for detecting active small bowel inflammation, although image quality across the study cohort appeared to be better with CTE. Improved soft tissue contrast with MRI provided by the combination of T2/T1 postcontrast and diffusion-weighted images has the potential to allow a better assessment of the relative inflammation versus fibrosis burden in strictureing Crohn’s disease, although the utility of this characterization is still being studied. MRI is also able to provide functional motility information, which may have a role in surgical planning. Although imaging modalities are evolving, currently, MRE appears to be a comparable alternative to CTE, in particular when radiation exposure is a concern, and
provide complementary information to ileocolonoscopy in the diagnosis of Crohn’s disease.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for small bowel Crohn’s disease includes irritable bowel syndrome, acute appendicitis, intestinal ischemia, pelvic inflammatory disease, endometriosis, and gynecologic malignancies. Other disorders that are within the differential diagnosis include radiation enteritis, *Yersinia* infections, intestinal injury from nonsteroidal anti-inflammation agents, intestinal tuberculosis, and small bowel tumors.

Among the most important ailments to consider are small bowel malignancy and intestinal tuberculosis. In patients in whom small bowel malignancy is suspected, resection should be undertaken to make certain the diagnosis. The exclusion of intestinal tuberculosis can be difficult, as the inflammation and stricturing of the terminal ileum can occur in a manner that closely mimics Crohn’s disease. The patient should be assessed for exposure to tuberculosis and screened for tuberculosis with a purified protein derivative skin test. Chest radiography should also be considered. Even when the diagnosis of Crohn’s disease is certain, patients who coincidentally are found to also have latent tuberculosis should be treated in accordance with American Thoracic Society guidelines prior to the initiation of immunosuppressive therapy for management of their Crohn’s disease.\(^{72}\)

Intestinal injury from nonsteroidal anti-inflammatory drugs (NSAIDs) can result in focal enteritis with ulceration and stricture formation.\(^{73,74}\) These manifestations can be very difficult to distinguish from Crohn’s disease of the small bowel. This rare side effect from the commonly used NSAIDs often requires resection or biopsy to confirm the diagnosis.

For Crohn’s disease of the colon, the differential diagnosis includes ulcerative colitis, infectious colitis, collagenous colitis, ischemic colitis, diverticular disease, Behçet disease, colonic neoplasm, solitary rectal ulcer syndrome, and NSAID colopathy.

The entity that is most difficult to distinguish from Crohn’s colitis is ulcerative colitis. The diagnosis of ulcerative colitis cannot be made with absolute certainty, as it is possible for Crohn’s disease of the colon to reproduce all the features of ulcerative colitis. It is only when features appear
that are unique to Crohn’s disease that the diagnosis of Crohn’s disease can be made. Such distinguishing features of Crohn’s disease include small bowel involvement, perianal disease, skip lesions, transmural inflammation, fistulas, abscesses, and noncaseating granulomas. After a complete history and physical examination complemented by appropriate radiologic, endoscopic, and humoral studies, Crohn’s disease and ulcerative colitis can be distinguished with a high degree of confidence in as many as 85% to 90% of cases, yet in the remaining 10% to 15% of cases, the differential diagnosis will remain indeterminate.

MEDICAL MANAGEMENT

The goal of medical treatment of Crohn’s disease is to provide long-lasting symptomatic relief while avoiding excessive morbidity. Crohn’s disease cannot be cured by medical treatment, but it may afford long periods of disease control and avoidance of surgical intervention. Thus, it is important that the surgeon have an understanding of the basics of medical therapy for Crohn’s disease. Selecting the optimal medical treatment for each individual requires experience and special expertise because of the variable course of the disease, the myriad of different clinical presentations and associated complications, and the desire to optimize medical treatment for each clinical situation. Multiple different medical therapies are used for the treatment of Crohn’s disease and depend on the location and severity of the disease as well as goals of treatment (induction vs maintenance of remission).

5-Aminosalicylic Acid

The aminosalicylates as a group of medications include sulfasalazine and 5-aminosalicylic acid (5-ASA) derivatives. The exact mechanism of action for these agents is not clear, but 5-ASA is thought to function through various pathways. 5-ASA compounds inhibit leukotriene production by inhibition of 5-lipoxygenase activity. 5-ASA also inhibits the production of interleukin-1 and tumor necrosis factor (TNF). 5-ASA compounds are weak inhibitors of cyclooxygenase (COX) activity, and it is unlikely that they act through the inhibition of prostaglandin production. Aminosalicylates are effective in the treatment of mild to moderate Crohn’s disease. 5-ASA given
in a controlled-release preparation is also effective as maintenance therapy to prevent recurrence after a flare of disease has been effectively managed either medically or surgically.⁷⁶-⁷⁹

Aminosalicylates come in a variety of preparations, each designed to deliver the drug in a topical fashion to the affected segments of intestine.⁸⁰ For instance, Asacol (mesalamine) is 5-ASA contained within a pH-dependent resin designed to release the drug in the terminal ileum and colon where the pH is typically greater than 7.0. Pentasa (mesalamine) is 5-ASA contained within ethylcellulose-coated microgranules designed to slowly release the active compound throughout the entire small bowel and colon. Colazal (balsalazide) is 5-ASA bound to an inert carrier by an AZO bond. This bond is broken by bacterial enzymes found within the colon, releasing the active 5-ASA compound to the colonic mucosa. The most common side effects are headache, fever, rash, and reversible infertility in men; a rarer complication is pancreatitis.

It is important to emphasize that mesalamine and its derivatives should not be confused with acetylsalicylic acid (aspirin) and other NSAIDs. Unlike 5-ASA compounds, classic NSAIDs are powerful inhibitors of COX-1 and COX-2. Many clinicians have had concerns that NSAIDs may exacerbate Crohn’s disease.⁸¹-⁸³ Although the basis of these concerns has been challenged,⁸⁴,⁸⁵ it is recommended that patients with Crohn’s disease avoid NSAIDs and use alternative medications when appropriate.

**Antibiotics (Ciprofloxacin/Metronidazole)**

Antibiotics have a well-established role in the management of septic complications of inflammatory bowel disease such as abscesses or wound infections. They may be used in the maintenance therapy of chronic perineal septic complications and in the treatment of bacterial overgrowth associated with chronic obstructive disease of the small bowel. Their benefit in primary treatment of Crohn’s disease is not well established, although they are commonly used in clinical practice.⁸⁶

**Corticosteroids**

Corticosteroids are the most effective agents for controlling acute
exacerbations of Crohn’s disease, but their use is limited due to the risk of serious side effects. The majority of patients with active small bowel Crohn’s disease will experience clinical remission with a short course of oral prednisone given in a dose between 0.25 and 0.5 mg/kg/d.\textsuperscript{87} For patients unable to take oral medications, methylprednisolone can be administered in the adult at doses of 40 to 60 mg given as a daily infusion.\textsuperscript{88} Common side effects from corticosteroids include diabetes, osteoporosis, cataracts, osteonecrosis, myopathy, psychosis, opportunistic infections, and adrenal suppression. The risks for these side effects are related to both the dose and the duration of steroid therapy.

**Immunomodulators (Azathioprine and 6-Mercaptopurine)**

Azathioprine and 6-mercaptopurine (6-MP) are immunosuppressive agents that inhibit cytotoxic T-cell and natural killer cell function. These agents have been shown to be effective in treating mild to moderate Crohn’s disease.\textsuperscript{88,89} Azathioprine given at 2.0 to 2.5 mg/kg/d or 6-MP in doses of 1.0 to 1.5 mg/kg/d will result in a 50\% to 60\% response rate in patients with active Crohn’s disease.\textsuperscript{88,90} Both 6-MP and azathioprine are also effective in maintaining remission following surgery or successful medical management.\textsuperscript{77}

**Biologic Therapies (Anti-TNF Therapies and Anti-Integrin Antibodies)**

Three anti-TNF therapies are approved for treatment of Crohn’s disease in adults in the United States, and all have been shown to be effective for treatment of GI manifestations of Crohn’s disease. Indirect evidence suggests that there are no significant differences in efficacy between these 3 anti-TNF therapies; however, no randomized controlled trials have directly compared them.\textsuperscript{91}

Infliximab, the best studied, is a chimeric mouse-human monoclonal antibody to TNF. TNF is a proinflammatory cytokine that is believed to be important in the pathophysiology of Crohn’s disease. Infliximab binds to both
free and membrane-bound TNF and prevents TNF from binding to its cell surface receptors. Clinical trials have demonstrated an 80% response rate with a single dose of infliximab. It is important to note that the doses and dosing intervals of infliximab must be individualized, but a typical regimen would include 5 mg/kg of infliximab given intravenously at weeks 0, 2, and 6, with a dose of 5 mg/kg every 8 weeks thereafter.

Because anti-TNF drugs are potent immunosuppressive agents, concerns have been raised about the risk for poor wound healing and postoperative septic complications. Current available data on the perioperative risks are somewhat conflicting. Early studies have suggested that preoperative anti-TNF drug use does not appear to increase the risk for postoperative complications following abdominal surgery for Crohn’s disease. More recently, however, a study from the Cleveland Clinic demonstrated an increased risk for infectious complications and intra-abdominal abscesses in Crohn’s disease patients undergoing surgery who received infliximab. This study also found that the presence of a diverting stoma significantly decreased the risk for septic complications in patients who had been treated with anti-TNF drugs.

Although experience with anti-integrin therapies is still slight, there are several promising drugs on the horizon. Natalizumab is an anti-alpha-4 integrin and blocks leukocyte migration to areas of inflammation. The effectiveness of natalizumab was confirmed in the Encore trial, in which 509 patients with moderate to severe active Crohn’s disease were randomized (1:1) to receive natalizumab 300 mg versus placebo. An improved response was seen in 48% of the natalizumab-treated patients compared to 32% of the patients receiving placebo (P = .001) Vedolizumab is a humanized anti-α4-β7 integrin monoclonal antibody that may help in moderated to severe Crohn’s disease and was recently approved by the US Food and Drug Administration. Ustekinumab is a human IgG monoclonal antibody that blocks the activity of interleukin (IL)-12 and IL-23 and has shown benefit in patients resistant to TNF antagonists. Additional monoclonal antibodies are being investigated and show promise.

**Other Medical Therapies**

Other agents that are used with varying success in the treatment of Crohn’s
disease include methotrexate, cyclosporine, tacrolimus, and thalidomide. Each of these agents requires a complete and sophisticated knowledge of appropriate dosing, side effects, therapeutic efficacy, and toxicities, which is beyond the scope of this chapter. These medications are often used in conjunction with the more standard medications.

**SURGICAL TREATMENT**

Similar to medical treatment, the goal of surgical treatment of Crohn’s disease is to provide long-lasting symptomatic relief while avoiding excessive morbidity. Crohn’s disease cannot be cured by surgical therapy, and thus surgery, like medical treatment, should be considered palliative. Complete extirpation of disease should not be the primary goal of surgery, as this does not produce cure and is frequently counterproductive. Rather, treatment of complications and palliation of symptoms while avoiding excessive loss of intestine should be the main aims of surgical treatment.

To avoid excessive loss of intestine, nonresectional techniques such as strictureplasty may be required. Additionally, optimal surgical therapy may require leaving behind segments of the intestinal tract affected by mild but asymptomatic disease with resection of only the areas of severe and symptomatic Crohn’s disease. The best surgical strategy for each patient with Crohn’s disease takes into account the indications for surgical treatment and the natural history of the disease, with its high risk for recurrence and the need for repeated surgeries.

**Indications for Surgery**

**FAILURE OF MEDICAL TREATMENT**

The failure to respond to medical treatment and the inability to tolerate effective therapy are the most common indications for surgical treatment of Crohn’s disease. Some patients may respond to the initial medical therapy only to rapidly relapse with tapering of the medical treatment. For example, some patients respond well to steroid therapy but become steroid dependent as tapering of the steroid dose results in recurrent symptoms. Because of the severe complications that are virtually inevitable with prolonged steroid treatment, surgery is warranted if the patient cannot be weaned from systemic
steroids within 3 to 6 months. The occurrence of complications related to the medical treatment or the progression of disease while on maximal medical treatment represent additional indications for surgical treatment.

**INTESTINAL OBSTRUCTION**

Partial or complete intestinal obstruction is a common indication for operation for Crohn’s disease. The clinical presentation of chronic partial small bowel obstruction is much more typical than complete obstruction. Patients with chronic partial small bowel obstruction due to Crohn’s disease may experience postprandial cramps, abdominal distension, borborygmi, and weight loss. To avoid symptoms, many patients will restrict their diets to soft foods or even liquids. If partial obstruction from Crohn’s disease is primarily due to acute inflammation and bowel wall thickening, initial medical therapy is warranted. If, however, the obstructive symptoms are due to high-grade fibrostenotic lesions, medical treatment will not reverse these lesions and surgery is indicated.

When complete intestinal obstruction occurs, initial conservative treatment with nasogastric decompression and intravenous hydration is warranted. Intravenous steroids are also administered. This allows for decompression of acutely distended and edematous bowel and, in most cases, for resolution of the complete obstruction. Resolution of the complete obstruction should not lead the physician to attempt treating the patient with continuing medical therapy. Patients with complete obstruction who respond well to initial conservative therapy are at high risk for persistent or recurrent symptoms of obstruction and are best managed with surgery once adequate decompression is achieved. The surgery can be performed under elective and safer conditions after appropriate bowel preparation.

**FISTULAS**

Intestinal fistulas occur in one-third of Crohn’s disease patients. Intestinal fistulas, however, are the primary indication for surgery in only a minority of patients. Thus, the presence of an intestinal fistula is not in and of itself an indication for surgery. In general, intestinal fistulas are the primary indication for surgical treatment if they connect with the genitourinary tract, if their drainage is cause for personal embarrassment and discomfort.
(enterocutaneous and enterovaginal fistulas), or if they create a bypass of such magnitude as to cause intestinal malabsorption.

Fistulas between the ileum and the urinary bladder often result in recurrent urinary tract infections, including pyelonephritis. While it is not mandatory to operate on all cases of enterovesical fistulas, surgery is warranted to avoid deterioration of renal function with recurrent infections or if symptoms persist despite appropriate medical therapy.

Enterocutaneous fistulas and enterovaginal fistulas often cause physical discomfort and personal embarrassment. A trial of medical therapy may be elected for enterocutaneous and enterovaginal fistulas, but most such cases will require surgery.  

Occasionally, an enteroenteric fistula can result in significant symptoms. Fistulas that result in functional bypass of a major intestinal segment can result in malabsorption or diarrhea. These fistulas need to be addressed surgically.

ABSCESSES AND INFLAMMATORY MASSES

Intra-abdominal abscesses and inflammatory masses occur less frequently than fistulas but are more often an indication for operative intervention. Small abscesses seen on CT may warrant a trial of treatment with antibiotics, but almost all intra-abdominal abscesses will require drainage. In a vast majority of cases, Crohn’s abscesses can be drained percutaneously with CT or ultrasound guidance. The rare large intraloop abscesses may require open surgical drainage. Often, in such cases, the abscess can be completely extirpated with the resection of the diseased segment of intestine.

Crohn’s abscesses usually originate from a severely diseased segment of bowel. A Crohn’s abscess that has been drained percutaneously is very likely to recur or result in an enterocutaneous fistula, and surgical resection is often advised even after successful drainage. Inflammatory masses indicate severe disease and often harbor an unrecognized abscess. Thus, inflammatory masses that do not readily respond to antibiotic treatment should be considered for surgical treatment.

PERFORATION

Free perforation is a rare complication of Crohn’s disease, occurring in fewer
than 1% of cases.\textsuperscript{110} When this complication occurs, it is an obvious indication for urgent operation. The diagnosis of free perforation is made by detecting a sudden change in the patient’s symptoms along with the development of the physical findings of peritonitis or the identification of free intraperitoneal air as demonstrated on plain x-rays or CT scans. The use of immunosuppressants and glucocorticosteroids can blunt many of the physical findings of acute perforation; therefore, the index of suspicion for perforation must be higher in immunocompromised patients who complain of worsening symptoms or show early signs of sepsis. Most patients, however, will demonstrate classic signs of peritonitis with rebound, rigidity, guarding, and loss of bowel sounds.

**HEMORRHAGE**

Hemorrhage is an uncommon complication from Crohn’s disease. Massive GI hemorrhage is rare and occurs more frequently from Crohn’s colitis than in small bowel Crohn’s disease.\textsuperscript{111} Hemorrhage from small bowel Crohn’s disease tends to be indolent with episodic or chronic bleeding requiring intermittent transfusions, but it rarely requires emergent surgery. Localization of the site of bleeding is accomplished by angiography in the presence of brisk bleeding; otherwise, colonoscopy can be attempted preoperatively to localize a source of lower GI hemorrhage. Intraoperative localization can be aided by enteroscopy or colonoscopy.

When severe hemorrhage occurs in Crohn’s disease, it is usually due to erosion of a single vessel by a deep ulcer or fissure. Recurrent bleeding in an area of small bowel disease is a common phenomenon, and it has been argued that even after control of hemorrhage from small bowel Crohn’s disease with conservative management, elective resection of the areas of Crohn’s disease should be undertaken to prevent recurrent bleeding.

Patients with Crohn’s disease are also at risk for bleeding from peptic ulcer disease. This is particularly true for patients receiving corticosteroid therapy. For this reason, Crohn’s disease patients who develop GI bleeding should undergo an upper endoscopy to rule out gastric or duodenal ulcers.

**CANCER OR SUSPICION OF CANCER**

The presence of Crohn’s disease increases the risk of adenocarcinoma of the
The diagnosis of adenocarcinoma of the small bowel is difficult because symptoms and radiographic findings of small bowel malignancy can be similar to those of the underlying Crohn’s disease. Male patients and patients with long-standing disease appear to be at increased risk for small bowel adenocarcinoma. Defunctionalized segments of bowel also seem to be at particular risk for malignancy. For this reason, bypass surgery should be avoided for Crohn’s disease of the small intestine, and defunctionalized rectal stumps should either be restored to their function or excised.

Adenocarcinoma of the small intestine should be suspected in any patient with long-standing disease whose symptoms of obstruction progress after a lengthy quiescent period. Surveillance for colonic malignancies can be undertaken by colonoscopy with random mucosal biopsy. If dysplasia is encountered, resection of the areas of Crohn’s disease should be considered. Areas of stricture formation within the colon should be closely examined and biopsied. Strictures that are too narrow to allow passage of the colonoscope or cannot be adequately assessed colonoscopically should be resected or biopsied if a stricturoplasty is performed.

GROWTH RETARDATION

Growth retardation occurs in a quarter of children affected by Crohn’s disease. Although steroid treatment may delay growth in children, the major cause of growth retardation in Crohn’s disease patients is the malnutrition associated with active intestinal disease.

Preoperative Preparation and Evaluation

A complete assessment of the GI tract is required prior to surgery. Full delineation of the extent of disease and associated complications is necessary to plan for the optimal surgical strategies.

Assessment of the small intestine can be performed with a small bowel follow-through, an enteroclysis study, MRE, or CTE. The colon and rectum are best evaluated by colonoscopy. Barium enema studies can also be used to evaluate for colonic disease, particularly in cases in which strictures do not
allow passage of the colonoscope. If the patient has had a previous resection of the ileocecal valve, a contrast enema can be a useful means of evaluating the ileocolonic anastomosis and the preanastomotic segment for recurrent disease. If an abscess, fistula, or inflammatory mass is suspected, a CT scan of the abdomen and pelvis with both oral and intravenous contrast should be obtained. CTE combined with ileocolonoscopy is used by many as a first-line test for the staging of Crohn’s disease. In patients in whom urgent surgery is required, a full evaluation of the GI tract prior to surgery may not be feasible. In these cases, evaluation of disease must be accomplished intraoperatively, and both the patient and the surgeon must be prepared for a wide variety of surgical possibilities.

As with preparation for any major operation, metabolic derangements must be treated prior to surgery. Fluid and electrolyte abnormalities must be corrected. Patients with profound anemia need to be transfused, and coagulopathies must be addressed. Patients with cardiovascular or pulmonary disease should have the condition stabilized and their functional capacity optimized prior to operation. Most patients with Crohn’s disease will not require preoperative parenteral nutrition, as most suffer from only a minor degree of malnutrition. There are rare cases, however, in which the nutritional status of the patient has been so severely compromised that they benefit from several weeks of bowel rest, parenteral nutrition, and ongoing medical treatment before operation.

The absolute need for mechanical bowel preparation is controversial. Traditionally, mechanical bowel preparations have been an unquestioned standard to lessen the risks of sepsis and to allow for a safe anastomosis. Recently, these advantages have been challenged. Even so, it is common practice for patients undergoing intestinal resection for Crohn’s disease to undergo a complete mechanical bowel preparation with either polyethylene glycol or sodium phosphate. Should the patient be unable to tolerate oral preparations, enemas can be used. Prophylactic broad-spectrum antibiotics are administered perioperatively, and stress dose steroids must be given to patients suspected of hypothalamic-pituitary-adrenal suppression. If feasible, well-contained intra-abdominal abscesses should be drained percutaneously prior to surgery. If an abdominal stoma is contemplated, the optimal site for the stoma location should be marked preoperatively. In patients in whom preoperative CT scan suggests significant inflammation in
proximity to the ureters, preoperative ureteral stenting can be helpful.

Some have suggested that, to improve the safety of surgery for Crohn’s disease, anti-inflammatory Crohn’s medication should be either lowered or discontinued prior to elective surgery. Recent studies, however, have shown that preoperative use of steroids and antimetabolites does not appear to affect the perioperative morbidity, and hence, discontinuation of these medications is not likely to result in significant benefit. Methotrexate and infliximab, on the other hand, are 2 medications that may be worth discontinuing at least 2 weeks and 2 to 3 months, respectively, prior to surgery. Laboratory studies have shown decreased wound healing with methotrexate, and clinical data to evaluate the safety of methotrexate in patients undergoing bowel resection with anastomosis are lacking. A recent study from the Cleveland Clinic has demonstrated an increased risk for infectious complications and intra-abdominal abscesses after recent treatment with infliximab.

Surgical Options

INTESTINAL RESECTION

Intestinal resection with anastomosis or stoma formation is the most common surgical procedure performed for the treatment of Crohn’s disease. Most cases of Crohn’s disease require only limited resections that are generally well tolerated and do not place these patients at risk for short bowel syndrome. Cumulative clinical data including randomized studies have indicated that resection of Crohn’s disease need only encompass the grossly apparent disease, as wider resections do not improve the outcome after surgery. Microscopic resection margins that are grossly normal but demonstrate microscopic evidence for Crohn’s activity do not result in early recurrence or other complications. Hence, intraoperative frozen section of the resection margins is not necessary.

The extent of mesenteric dissection does not affect the long-term results either; hence, the mesentery can be divided at the most advantageous level. Division of the thickened mesentery of small bowel Crohn’s disease can be the most challenging aspect of the procedure. Identification and isolation of individual mesenteric vessels are not feasible with a thickened Crohn’s mesentery. Although many approaches to this problem have been described, a common technique is to apply overlapping clamps on either side of the
intended line of transection. The mesentery is then divided between the clamps, and the tissue contained within the clamps is suture-ligated (Fig. 45-4). In severe cases, a vascular clamp may be used at the root of the small bowel mesentery to obtain proximal control: mattress sutures may then need to be applied to the cut edge of the mesentery to control bleeding. The use of tissue welding devices can be useful for sealing vessels within the thickened mesentery. Even with these devices, mattress sutures in the mesentery are commonly needed for complete hemostasis. Despite the difficulty dealing with the thickened and often hyperemic mesentery, resection can be performed with a low risk for postoperative hemorrhage, and the risk for postoperative hemoperitoneum requiring reexploration has been reported to be less than 0.5%. 99

FIGURE 45-4 Technique for division of thickened Crohn’s mesentery.

ANASTOMOSIS

There is no overriding consensus regarding the optimal technique for intestinal anastomosis in Crohn’s disease. 76,128-132 It is well established that recurrent Crohn’s disease after resection of terminal ileal disease is most
likely to occur at the ileocolonic anastomosis or at the preanastomotic ileum. It has been proposed that large-caliber anastomoses require a longer period to stricture down to a critical diameter that becomes symptomatic. The argument is made that a longer side-to-side anastomosis may be beneficial over an end-to-end or end-to-side anastomosis.\textsuperscript{131} To date, however, clinical data do not indicate a benefit for one particular intestinal configuration over another.\textsuperscript{130} Intestinal anastomosis for Crohn’s disease cases can be fashioned with a stapling device or may be hand-sutured. When performed under selective conditions, resection with primary anastomosis for Crohn’s disease can be performed with a high degree of safety, and small bowel anastomotic dehiscence rates can be kept under 1%.\textsuperscript{99} In the presence of sepsis, severe scarring, malnutrition, or recent use of methotrexate or infliximab, it may be wise to protect the anastomosis with a proximal loop stoma or to forego the anastomosis altogether and bring out an end stoma at the point of resection.

**STOMA FORMATION**

Permanent stomas are required for the surgical treatment of Crohn’s proctitis and occasionally required for the management of severe, unrelenting perianal disease. Temporary stomas are much more common and typically used as a means of protecting a distal anastomosis or when an anastomosis is not advisable.

If an ileostomy or colostomy is contemplated, selection of the optimal placement of the stoma should be determined preoperatively.\textsuperscript{133} Proper stoma location is critical to achieve a satisfactory stoma. It is preferable to locate the ileostomy over the left or right rectus abdominis muscle on a flat area away from deep skin folds and bony prominences.\textsuperscript{134} The surface of the abdomen must be evaluated in both the sitting and standing positions, as this will often demonstrate skin folds and creases not evident in the supine position. Attention must be paid to determining the level of the patient’s belt line, and every effort is made to place the stoma below it. Once the optimal position of the stoma has been identified, it is marked in a manner that will remain visible at the time of surgery.

Complications related to intestinal stomas are common. They include peristomal hernia, prolapse, and stricture. Peristomal hernia is the most common ostomy-related complication. It can be anticipated that approximately 25% of patients with a permanent stoma will require surgical
revision of their ostomy to deal with 1 or more of these complications.\textsuperscript{135}

**BYPASS PROCEDURES**

Bypass procedures became popular in the 1940s and 1950s once physicians and surgeons realized that aggressive enterectomies did not reduce the incidence of recurrence and were fraught with the development of short gut syndrome. Initially conceived to bypass an area of stricture or obstruction, the use of bypass procedures was eventually extended to Crohn’s disease complicated by septic complications. Increased experience with bypass procedures revealed that persistence of disease put patients at risk of persistent sepsis and eventually neoplastic transformation. Because of these complications, bypass procedures were supplanted by limited intestinal resection as the main surgical option in the late 1960s in all intestinal districts except the duodenum, where a simple side-to-side retrocolic gastrojejunostomy adequately relieves the obstructive symptoms. With increased experience and confidence in the performance of strictureplasty, duodenal disease is now more often managed using strictureplasties.

**STRUCTUREPLASTY**

Strictureplasty techniques have gained popularity as a safe and effective means of treating stricturing Crohn’s disease of the small intestine without resorting to lengthy resections. Strictureplasties are best used when resection would otherwise result in loss of a lengthy segment of bowel and thus place the patient at risk for short bowel syndrome. This would include cases with long segments of stricturing disease and patients with multiple prior resections. They are also indicated when they offer a simpler alternative to resection, such as in short recurrent disease at a previous ileocolic or enteroenteric anastomosis.

It is generally accepted that the advantage conferred by a strictureplasty over a resection in the preservation of intestinal absorptive capacity is mainly due to the sparing of normal areas in between strictures that would be otherwise sacrificed. Although this is true, there is increased evidence that the acuity of the disease decreases at the site of the strictureplasty and the disease becomes quiescent and may have a lower rate of recurrence of disease.\textsuperscript{136} Whether this correlates with a simultaneous restoration of absorptive function
has not yet been established. The most commonly performed strictureplasty is the Heinecke-Mikulicz strictureplasty.\textsuperscript{137-139} The Heinecke-Mikulicz is named after the pyloroplasty technique from which this procedure is derived. With the Heinecke-Mikulicz strictureplasty, a longitudinal incision is made along the antimesenteric border of the stricture (Fig. 45-5). This incision should extend for 1 to 2 cm into the normal elastic bowel on either side of the stricture. Once the enterotomy is made, the area of the stricture should be closely examined. If there is any concern that the stricture may harbor a malignancy, a biopsy with frozen section must be obtained. Complete hemostasis should be obtained with precise application of electrocautery. The longitudinal enterotomy of the Heinecke-Mikulicz strictureplasty is then closed in a transverse fashion. The closure can be accomplished with either single- or double-layered sutures. The Heinecke-Mikulicz stricture technique is appropriate for short-segment strictures of 2 to 5 cm in length.
The Finney strictureplasty, also named for the pyloroplasty technique from which this approach is derived, can be used for strictures up to 15 cm in length. With the Finney strictureplasty technique, the strictured segment is folded onto itself in a U-shape (Fig. 45-6). A row of seromuscular sutures is placed between the 2 arms of the U, and a longitudinal U-shaped enterotomy is then made paralleling the row of sutures. The mucosal surface is examined, and biopsies are taken as necessary. Homeostasis is obtained with electrocautery. Full-thickness sutures are then placed beginning at the posterior wall of the apex of the strictureplasty and then continued down to
approximate the proximal and distal ends of the enterotomy. This full-thickness suture line is then continued anteriorly to close the strictureplasty. To complete the procedure, a row of seromuscular Lembert sutures is placed anteriorly. In essence, the Finney is a short side-to-side functional anastomosis. A very long Finney strictureplasty may result in a functional bypass with a large lateral diverticulum. This diverticulum, in theory, could be at risk for bacterial overgrowth and the blind loop syndrome. Fortunately, this theoretical concern has not been observed in clinical practice.

FIGURE 45-6 Finney strictureplasty.

The purpose of the strictureplasty is to preserve intestinal length that otherwise would be sacrificed with resection. Those cases with long segments of stricturing disease are the ones in which nonresectional methods should be aggressively pursued. To manage such cases, multiple strictureplasties are typically required. In general, however, repeated Heinecke-Mikulicz or Finney strictureplasties should be separated from each other by at least 5 cm. Otherwise, the result can be a bulky and relatively unyielding segment of intestine with considerable tension placed on each suture line.

Patients with multiple strictures grouped close together are best managed with a side-to-side isoperistaltic strictureplasty, also called Michelassi strictureplasty. With this technique, the segment of stricturing disease is divided at its midpoint. The proximal and distal ends are then drawn onto
each other in a side-to-side fashion (Fig. 45-7). Division of some of the mesenteric vascular arcades facilitates the positioning of the 2 limbs over each other. The proximal and distal loops are then sutured together with a layer of interrupted seromuscular sutures. A longitudinal enterotomy is then made along both of the loops (Fig. 45-8). The intestinal ends are spatulated to provide a smoothly tailored fit to the ultimate closure of the strictureplasty. Again, this is the time to examine the mucosal surface of the intestine to detect potential areas of neoplastic transformation and control bleeding. The outer suture line is reinforced with an interior row of either interrupted or running full-thickness sutures. This inner suture line is continued anteriorly. The anterior closure is then reinforced with an outer layer of interrupted seromuscular sutures to complete the strictureplasty (Fig. 45-9).

FIGURE 45-7 Isoperistaltic side-to-side strictureplasty. The segment of intestine affected by Crohn’s strictures is divided, and the 2 limbs are drawn onto each other.
FIGURE 45-8  Isoperistaltic side-to-side strictureplasty. Longitudinal enterotomies are made along the antimesenteric borders of the 2 limbs.
FIGURE 45-9  Isoperistaltic side-to-side strictureplasty. The 2 limbs are anastomosed together in a lengthy side-to-side fashion.

Originally described in 1996, this procedure has been used with increasing frequency. The isoperistaltic side-to-side strictureplasty is recognized as an effective means of treating extensive small bowel Crohn’s disease and provides the best option for those cases that would otherwise require extensive intestinal resection with loss of significant length of small bowel.\textsuperscript{136,139,142,143}

Unlike resection, diseased segments are retained with strictureplasty, and suture lines are placed in Crohn’s disease–affected tissue. This has been a cause of concern regarding the risk of intestinal suture line dehiscence, long-term recurrences, and risk for malignancy. The ongoing and now substantial clinical experience with these techniques has allayed these concerns.\textsuperscript{144} In appropriately selected patients, perioperative morbidity from strictureplasty appears to be similar to that of resection and primary anastomosis. Specifically, intestinal suture line dehiscence appears to be uncommon with any of the described strictureplasty techniques.\textsuperscript{145,146} The most common postoperative complication directly related to strictureplasty is hemorrhage.
from the strictureplasty site. This has been reported to occur in up to 9% of cases. Fortunately, the GI hemorrhage following strictureplasty is typically minor and can be managed conservatively with transfusions alone. Rarely, more persistent bleeding may require intra-arterial infusion of vasopressin, but the need for reoperation to control hemorrhage after strictureplasty is very rare. It is by now also well established that strictureplasty techniques provide excellent long-term symptomatic relief that is comparable to resections with anastomosis. Although there are no controlled studies directly comparing strictureplasty to resection, multiple reports of the observed symptomatic recurrence rates after strictureplasty compare well with published recurrence rates after resection and anastomosis.\textsuperscript{139,146,147}

Epidemiologic studies have shown an increased risk for small bowel adenocarcinoma in Crohn’s disease patients.\textsuperscript{114} This risk is increased in patients with long-standing disease. It is not known if strictureplasty by virtue of its retention of diseased tissue increases this risk. At the time of the writing of this chapter, there have been only 2 reported cases of an adenocarcinoma developing at a site of previous small bowel strictureplasty, and thus, it is believed that the risk of malignancy after strictureplasty is low.\textsuperscript{148,149}

### Laparoscopy

Over the past 2 decades, laparoscopy has been dramatically changing all aspects of GI surgery. Specifically in colon and rectal surgery, laparoscopy has been widely used in benign disease,\textsuperscript{150,151} including inflammatory bowel disease, and more recently in colon cancer.\textsuperscript{152} Several single-institution small reports suggest that not only is laparoscopic surgery for Crohn’s disease feasible and safe but also it reduces length of hospitalization and recovery and allows for a smaller wound, with an overall reduction in morbidity.\textsuperscript{153-166}

Most patients with Crohn’s disease are well suited for laparoscopy. They are usually young, otherwise healthy, and interested in undergoing an operation that involves minimal scarring, because they face the risk of multiple major abdominal operations in their lifetime. On the other hand, Crohn’s disease represents a difficult arena even for the experienced open colorectal surgeon. Many of the unique features of Crohn’s disease, such as the intense inflammation and thickened mesentery, enteric fistula, inflammatory masses or abscesses, and multiplicity of areas of intestinal
involvement, have deterred many surgeons from even considering a laparoscopic approach.

Two prospective controlled studies have shown several advantages of the laparoscopic-assisted approach over the conventional approach.\textsuperscript{153,155} Bemelman and colleagues\textsuperscript{155} compared 48 open ileocolic resections with 30 laparoscopic-assisted resections. This study showed similarly low morbidity rates in both groups but a shorter hospital stay and improved cosmetic results in favor of the laparoscopic group.\textsuperscript{155} Alabaz and associates\textsuperscript{153} compared 48 open ileocolic resections with 26 laparoscopic-assisted resections. The patients in the laparoscopic group returned to work more quickly, had better cosmetic results, and were more likely to have improved postoperative quality of life.\textsuperscript{153} A prospective randomized trial comparing open and laparoscopic-assisted resections in 60 patients undergoing elective ileocecectomy for Crohn’s disease not complicated by abscess formation or complex fistula showed a faster postoperative recovery of respiratory function (measured as recovery of 80% of forced respiratory volume and forced vital capacity), shorter abdominal incisions, and longer performance time in the laparoscopic-assisted group. These differences were all statistically significant. With limited follow-up, there was no difference in recurrence rate.\textsuperscript{160} This study demonstrated that in experienced hands, morbidity from the laparoscopic approach compares favorably with that of a conventional open approach. Obviously these results need to be confirmed by larger series with longer follow-up.

The indications for laparoscopic surgery for Crohn’s disease should not differ from conventional open surgery, as described previously. Contraindications to a laparoscopic approach include patients who are critically ill and unable to tolerate the pneumoperitoneum due to hypotension or hypercarbia, patients with extensive intra-abdominal sepsis (abscess, free perforation, or complex fistula), and difficulty in identifying the anatomy (previous surgery, obesity, or adhesions). The same variety of surgical procedures described previously can be performed laparoscopically.

After induction of general anesthesia, the patient is placed on the operating table supine or in the modified lithotomy position. Rectal irrigation with diluted iodine solution is performed, especially in patients with involvement of the rectum and sigmoid colon. An epidural catheter is usually inserted at the time of surgery. The sympathetic blockade achieved with epidural
administration of local anesthetics and opioids prevents bowel distension, hence facilitating exploration of the GI tract and handling of the bowel. Depending on the procedure planned, 4 or 5 trocars are used, with the camera placed at the level of the umbilicus.

Every operation for Crohn’s disease, whether open or laparoscopic, should start with a complete examination of the entire GI tract starting from the ligament of Treitz. The patient is placed in the reverse Trendelenburg position and right lateral decubitus with the assistant standing on the patient’s left side retracting the transverse colon into the upper quadrants and the surgeon at the right of the patient or in between the patient’s legs, tracing the intestine from the ligament of Treitz all the way to the ileocolic pedicle. This maneuver is facilitated by progressively rotating the patient from the reverse Trendelenburg to a full Trendelenburg position and left lateral decubitus. In the presence of skip areas of involvement from Crohn’s disease, these are marked intracorporeally with sutures in order to facilitate retrieval of the diseased segments when the specimen is exteriorized.

Laparoscopic-assisted ileocolic resection is the most commonly performed laparoscopic procedure for Crohn’s disease. For laparoscopic ileoectomy, a 4-trocar technique is used (Fig. 45-10). Trocars of 5 mm can be used exclusively, as a 5-mm, 30-degree camera offers the same resolution as larger ones and the vascular pedicles can be divided intracorporeally with 5-mm instruments. After the bowel has been evaluated in its entirety as previously described, the assistant, standing on the right of the patient or in between the patient’s legs, places the ileocolic pedicle under tension with an intestinal grasper placed through the right lower quadrant trocar (Fig. 45-11). The surgeon on the patient’s left side dissects and divides it (Fig. 45-12). Once this is accomplished, a medial-to-lateral submesenteric mobilization of the ascending colon all the way to the hepatic flexure is completed (Fig. 45-13). When the submesenteric mobilization is completed, the lateral colonic peritoneal reflection is divided all the way to the hepatic flexure (Fig. 45-14). The terminal ileum is completely mobilized by dividing the peritoneum at the level of the pelvic rim to allow a tension-free anastomosis through a small incision. It is often necessary to completely mobilize the hepatic flexure without dividing the right branch of the ileocolic vessels in order to facilitate exteriorization of the specimen (Fig. 45-15). It is imperative to make sure that the mobilization is adequate before evacuating the pneumoperitoneum and making an incision to avoid a difficult anastomosis through a small incision.
or the need for a larger incision to exteriorize the specimen. Should this occur, a gel port can be applied through the abdominal incision to allow for creation of the pneumoperitoneum again and further intra-abdominal dissection.
FIGURE 45-10 Port site locations for laparoscopic ileocectomy.
FIGURE 45-11 Optimal position of the surgeons and assistants for laparoscopic ileocecectomy.
FIGURE 45-12 Laparoscopic isolation of the ileocolic vessels. (Reproduced with permission from the University of Chicago General Surgery Archives.)

FIGURE 45-13 Submesenteric mobilization of the ascending colon and
hepatic flexure with exposure of the duodenum. (Reproduced with permission from the University of Chicago General Surgery Archives.)

FIGURE 45-14 Division of the lateral peritoneal attachments to the ascending colon. (Reproduced with permission from the University of Chicago General Surgery Archives.)
Once the ileum, cecum, and ascending colon are fully mobilized, the instruments are removed. With the pneumoperitoneum still in place, the umbilical port site or the right lower quadrant port site is enlarged. The pneumoperitoneum is evacuated, and the specimen is exteriorized. The ileocolonic resection is then completed by dividing the remainder of the mesentery and the bowel extracorporeally. An anastomosis is then constructed in a standard fashion.

**Management of Complicated Crohn’s Disease**

**Crohn’s Disease of the Duodenum**

Primary Crohn’s disease of the duodenum almost always manifests with stricturing disease that can be managed by strictureplasty or with bypass procedures (Fig. 45-16). Fortunately, resection of the duodenum for Crohn’s disease is almost never required.\(^{167-169}\) Perforating Crohn’s disease almost never affects the duodenum. When the duodenum is involved with Crohn’s fistulas, it is always the result of disease within a distal segment (typically the terminal ileum or neoterminal ileum) that fistulizes into an otherwise normal duodenum.\(^{170}\) Yet, Crohn’s disease of the duodenum can offer a particularly challenging problem due to the retroperitoneal location of the organ and its intimate proximity to the pancreas.
Stricturing disease of the duodenum is often focal, and many cases can be managed with a strictureplasty.\textsuperscript{171} To safely accomplish a strictureplasty, the duodenum must be fully mobilized with a generous Kocher maneuver. Heinecke-Mikulicz strictureplasties can be safely performed in the first, second, and proximal third portion of the duodenum. Strictures of the last portion of the duodenum are better handled with a Finney strictureplasty constructed by creating an enteroenterostomy between the fourth portion of the duodenum and the first loop of the jejunum.

If the duodenal stricture is lengthy or the tissues around the stricture are
too rigid or unyielding, a strictureplasty should not be performed and an
intestinal bypass procedure should be undertaken. The most common bypass
procedure performed for duodenal Crohn’s disease is a simple side-to-side
retrocolic gastrojejunostomy.\textsuperscript{127} This procedure effectively relieves the
symptoms of duodenal obstruction related to Crohn’s strictures but carries a
high risk for stomal ulcerations. To lessen the likelihood of ulcerations
forming at the anastomosis, it has been recommended that a vagotomy be
performed along with the gastrojejunostomy.\textsuperscript{127} Because of the concerns of
vagotomy-related diarrhea, a highly selective vagotomy is preferred to a
truncal vagotomy. If the stricturing Crohn’s disease is limited to the third or
fourth portions of the duodenum, a Roux-en-Y duodenojejunostomy to the
proximal duodenum is preferred to a gastrojejunostomy.\textsuperscript{170} The Roux-en-Y
duodenojejunostomy has the advantage of bypassing strictures and eliminates
the concern regarding acid-induced marginal ulceration and the need for
vagotomy.

As noted previously, when the duodenum is involved with a Crohn’s
fistula, it is almost always the case that the diseased segment is located distal
in the GI tract, and the duodenum itself is otherwise free of active Crohn’s
disease.\textsuperscript{170} Most of these duodenal fistulas are small in caliber and
asymptomatic, but larger fistulas may shunt the duodenal contents to the
distal small bowel such that malabsorption and diarrhea result. In the
majority of cases, duodenoenteric fistulas are identified with preoperative
small bowel radiography; however, many are discovered only at the time of
surgery.\textsuperscript{172} With complex fistulizing disease involving an inflammatory
mass, great care at the time of surgery should be undertaken to limit the size
of the duodenal defect resulting from the resection of the fistula. Most
duodenal fistulas are located away from the pancreaticoduodenal margin, and
thus, these fistulas can be managed by resection of the primary Crohn’s
disease with primary closure of the duodenal defect. Larger fistulas or fistulas
that are involved with a large degree of inflammation may result in a sizable
duodenal defect. Such large defects may require closure with a Roux-en-Y
duodenojejunostomy or with a jejunal serosal patch.\textsuperscript{172,173} As noted
previously, duodenal resections are almost never necessary for Crohn’s
disease, and they should be considered the surgical option of last resort.

\textbf{Crohn’s Disease of the Small Bowel}
COMPLETE INTESTINAL OBSTRUCTION

Complete small intestinal obstruction resulting from Crohn’s disease only rarely requires urgent surgical intervention, as the vascular supply to the intestinal loop is never compromised and almost all cases of complete or high-grade partial small bowel obstruction from Crohn’s disease respond to conservative management. Such patients should be treated with nasogastric decompression, intravenous hydration, and steroid therapy. This approach allows for resolution of the acute episode of obstruction in a vast majority of cases. Unfortunately, most patients whose Crohn’s disease is severe enough to experience an episode of complete or high-grade partial obstruction are at high risk for recurrent episodes and persistent symptoms. For this reason, elective surgery should be considered once the episode of complete obstruction has resolved. The advantage of this approach is that surgery can be performed under safer conditions when the obstruction has resolved, the bowel is not distended or edematous, and an appropriate bowel preparation has been performed. If the obstruction fails to respond to appropriate conservative treatment, surgery is required. In these situations, the surgeon needs to have a high index of suspicion for small bowel cancer as the cause of the obstruction, as obstructions from cancers do not respond to bowel decompression and steroid treatment.

ILEOSIGMOID FISTULAS

Ileosigmoid fistula is a common complication of perforating Crohn’s disease of the terminal ileum. Typically, the inflamed terminal ileum adheres to the sigmoid colon that is otherwise normal and free of primary involvement of Crohn’s disease. Most ileosigmoid fistulas are small and do not produce any symptoms. Asymptomatic ileosigmoid fistulas do not in and of themselves require operative management. On the other hand, large ileosigmoid fistulas can result in bypass of the intestinal contents from the terminal ileum to the distal colon and thus give rise to debilitating diarrhea (Fig. 45-17). Such symptomatic fistulas often fail to respond to medical therapy and should be managed surgically.
More than half of the ileosigmoid fistulas from Crohn’s disease are not recognized prior to surgery. For this reason, the surgeon should be prepared to deal with this complication in any case of Crohn’s disease that involves the terminal ileum. Ileosigmoid fistulas can be managed by simple division of the fistulous adhesion and resection of the ileal disease. The defect in the sigmoid colon is then debrided, and simple closure is undertaken. In this manner, 75% of ileosigmoid fistulas can be managed. The remainder requires resection of the sigmoid colon. Sigmoid colon resection is necessary when primary closure of the fistula is at risk for poor healing. This is the case either when the sigmoid is also involved in Crohn’s disease, when the fistulous opening is particularly large, or when there is extensive fibrosis extending along the sigmoid colon. In addition, fistulous tracts that enter the sigmoid colon in proximity to the

![FIGURE 45-17](image-url)
mesentery can be difficult to close and often require resection and primary
anastomosis.

**ILEOVESICAL FISTULA**

Ileovesical fistulas occur in approximately 5% of Crohn’s disease patients.\(^9\) Hematuria and fecaluria are virtually diagnostic of ileovesical fistula, but these symptoms are absent in one-third of cases.\(^1\) Small bowel x-rays, cystograms, and cystoscopy often do not detect the fistula. Air within the bladder, as noted on CT scan, is often the best indirect evidence for the presence of an enterovesical fistula. An ileovesical fistula is an indicator of complex fistulizing disease, as most ileovesical fistulas occur along with other enteric fistulas. For example, as many as 60% of patients with an ileovesical fistula will also have an ileosigmoid fistula.\(^5\)

The necessity for surgery for ileovesical fistula is controversial. Many patients with ileovesical fistulas can be managed medically for extended periods of time without significant complications. Healing rates with medical treatment are not clearly defined, but they are probably low, and most patients with ileovesical fistulas will ultimately undergo surgery. Surgery is indicated when recurring urinary infections occur, particularly pyelonephritis, with concomitant potential for worsening of renal function.

Surgical treatment of ileovesical fistulas requires resection of the ileal disease with closure of the bladder defect. Most ileovesical fistulas involve the dome of the bladder, and thus debridement and primary closure can be accomplished without risk of injury to the trigone. Decompression of the bladder with an indwelling Foley catheter should be continued postoperatively until the bladder is confidently healed without leaks. A cystogram taken on postoperative day 5 is a convenient means for confirming the seal of the bladder repair and the safety of removing the Foley catheter.

**ENTEROVAGINAL AND ENTEROCUTANEOUS FISTULAS**

These are rare fistulas caused by perforating small bowel disease draining through the vaginal stump in a female who has previously undergone a hysterectomy or through the abdominal wall, usually at the site of a previous scar. These fistulas often require surgical intervention because they cause
physical discomfort and personal embarrassment. Surgical treatment requires resection of the small bowel disease. The vaginal cuff does not need to be closed; the chronic infection along the abdominal wall fistulous tract requires debridement and wide drainage to allow healing by secondary intention.

**ABSCESS**

Intra-abdominal abscesses that result from Crohn’s disease tend to follow an indolent course with modest fever, abdominal pain, and leukocytosis. Rapidly progressive and overwhelming sepsis is not typical for the clinical course of Crohn’s disease–related abscesses. In fact, in up to one-third of intra-abdominal Crohn’s abscesses, preoperative clinical signs of localized infection are absent and the abscesses are discovered only at the time of operation. When an abscess is suspected or an abdominal mass is palpated, a CT scan should be obtained, as 50% of tender intra-abdominal masses will harbor an abscess collection within. The CT scan can detect most chronic abscesses and can also delineate the size and location of the abscess as well as the relationship of the abscess to critical structures such as the ureters, duodenum, and the inferior vena cava (Fig. 45-18).

*FIGURE 45-18* CT scan of the pelvis demonstrating large Crohn’s abscess. (Reproduced with permission from the University of Chicago General Surgery Archives.)
Most abscesses with Crohn’s disease are in fact very small collections that are contained within the area of diseased intestine and its mesentery. In the case of small intraloop or intramesenteric abscesses, resection of the defective segment and its mesentery often extirpates the abscess such that drains are not necessary and primary anastomosis can be performed without risk.

Large abscesses related to Crohn’s disease are best managed with CT-guided percutaneous drainage.\textsuperscript{108} Percutaneous drainage is often very effective at controlling the sepsis and healing the abscess cavity.\textsuperscript{107} With percutaneous drainage of a Crohn’s disease abscess, an enterocutaneous fistula often occurs as the abscess typically connects to a deeply penetrating sinus emanating from a segment of Crohn’s disease–affected intestine. Percutaneous drainage then completes the fistulous tract from the intestine through the sinus to the abscess cavity and out the drain. Such a fistula may spontaneously close or it may persist, and the intestine may continue to be a source of sepsis. With successful drainage of the abscess, the sepsis often clears well enough that it can be tempting to try to manage the disease without subsequent surgery. Published clinical data on the optimal approach to such patients are unfortunately lacking. Even so, in the absence of Crohn’s symptoms, initial nonoperative management after successful percutaneous drainage can be undertaken in carefully selected patients.\textsuperscript{109} On the other hand, if drainage through the fistula continues, surgical resection of the affected segment of intestine becomes necessary.

**PERFORATION**

Free perforation is a surprisingly uncommon phenomenon because the chronic progressive inflammation of Crohn’s disease normally leads to adhesions with adjacent structures. Most perforations from Crohn’s disease occur in the ileum and are usually proximal to a stenotic lesion.\textsuperscript{110,127} The diagnosis of free perforation is made by detecting a sudden change in the patient’s symptoms along with the development of the physical findings of peritonitis or the identification of free intraperitoneal air as demonstrated on plain x-rays or CT scans. Free perforation is an absolute indication for emergent laparotomy with resection of the diseased segment and exteriorization of the proximal bowel as an end ileostomy. The distal bowel end can be exteriorized as a mucous fistula or closed as a defunctionalized
pouch, depending on the degree of peritoneal contamination. Creation of a primary anastomosis even with a proximal protecting loop ileostomy carries a high risk of anastomotic breakdown and should be avoided. Primary closure of the perforation should never be attempted, as sutures will not be able to approximate the edges of the perforated, edematous, and diseased bowel in a satisfactory and tension-free way and the presence of a distal intestinal stenosis or partial obstruction will cause an increase in the intraluminal pressure at the level of the local repair with subsequent dehiscence.

HEMORRHAGE

Hemorrhage from small bowel Crohn’s disease is managed by resection of the diseased portion of intestine. For patients with multiple skip areas of Crohn’s disease, small bowel angiography may be attempted to localize the exact site of bleeding. Localization with angiography may be unsuccessful if the bleeding is episodic or insufficiently brisk to be identified with angiography. In patients in whom small bowel hemorrhage stops spontaneously, the risk for rebleeding is high. Thus elective resection of active Crohn’s disease after the first episode of hemorrhage should be considered.

Crohn’s Disease of the Colon

The optimal management of Crohn’s disease of the colon is dependent on the distribution and the location of the disease (Fig. 45-19).
FIGURE 45-19 Contrast enema demonstrating severe Crohn’s colitis with multiple high-grade strictures. (Reproduced with permission from the University of Chicago General Surgery Archives.)

CECAL DISEASE

Colonic disease limited to the cecum is almost always associated with terminal ileal disease. The terminal ileitis is the predominant component of the ileocecal disease. Terminal ileal disease with extension into the cecum behaves much like disease limited to the terminal ileum. For this pattern of disease, surgical resection should encompass the margins of gross disease with an anastomosis between the neoterminal ileum and the proximal ascending colon. Recurrence of disease at the anastomosis or at the preanastomotic ileum is common, but the risk for recurrent disease within the distal colon or the rectum is low. This pattern of disease does not imply a
predisposition to more extensive colonic disease.

**RIGHT-SIDED COLITIS**

Disease involving the entire right colon can occur alone but more typically occurs along with disease of the terminal ileum. Extensive involvement of the right colon as a form of ileocolonic disease is less common than the ileocecal pattern. Surgical treatment involves a standard right hemicolecction to encompass the gross limits of the disease. An anastomosis between the ileum and the transverse colon is then fashioned. With a standard right hemicolecction, the anastomosis may rest in proximity to the duodenum. Recurrent disease at the preanastomotic ileum may thus secondarily involve the duodenum. This phenomenon can place the patient at risk for substantial morbidity should inflammatory encasement of the duodenum or fistulization into the duodenum occur. For this reason, it is advantageous to protect the duodenum by interposing omentum between the duodenum and the ileocolonic anastomosis.

**EXTENSIVE COLITIS WITH RECTAL SPARING**

Extensive colitis with sparing of the rectum occurs in approximately 20% of individuals suffering from Crohn’s colitis. In such cases, the rectum should be closely examined endoscopically, and, should the rectum be truly free of disease, a total abdominal colectomy with ileorectal anastomosis can be performed when fecal continence is adequate and the patient does not have extensive perineal septic complications. This procedure often results in good long-term function and enables many patients to avoid an ileostomy. Older patients or patients who have undergone an extensive small bowel resection may experience frequent and loose stools to the point that incontinence may develop after an ileorectal anastomosis. Additionally, recurrent disease within the rectum can result in significant deterioration of bowel function requiring further medical or even surgical intervention. Up to 50% of patients who undergo an ileorectal anastomosis for colonic Crohn’s disease will ultimately require a proctectomy with permanent ileostomy because of poor bowel function with incontinence or recurrence of disease in the rectum.

**PROCTOCOLITIS**
Surgical management of extensive involvement of the colon and rectum requires total proctocolectomy with permanent ileostomy in almost all cases. In most instances, a total proctocolectomy can be performed in a single step. The presence of severe perianal disease, however, may require that the procedure be performed in 2 stages. At the first stage, the intra-abdominal colon and majority of the rectum are removed and a short rectal stump is created at the level of the levator muscles. At the same time, perineal abscesses are drained and fistulas are laid open. This first step removes the diseased colon and rectum without creating a perineal wound that may be difficult to heal in the presence of active perineal sepsis. Once the perineal sepsis is cleared and the perineum is healed, the short anorectal stump can be removed through a perineal approach. At the second stage, primary closure of the perineum can be accomplished without the high risk of persistent perineal wounds.

Restorative procedures such as an ileal pouch–anal anastomosis or continent ileostomy have traditionally not been offered to patients who have Crohn’s colitis because of the recurrent nature of the disease. Even so, some of these procedures have been performed in patients whose diagnosis of Crohn’s disease was not known or suspected at the time of surgery. Various reports indicate that recurrence of Crohn’s disease within the pouch is common and removal of the pouch is often necessary. On the other hand, patients who do not suffer from recurrent disease generally do well and typically experience good pouch function.

While it is commonly accepted that restorative proctocolectomy with J-pouch ileoanal anastomosis should not be undertaken for Crohn’s colitis, there is a specific pattern of Crohn’s disease that appears to be at low risk for problems with recurrence after an ileoanal anastomosis. In cases in which Crohn’s disease is limited to the colon and rectum without any history of small bowel involvement and without any perineal manifestations, the risk for pouch failure after ileoanal anastomosis appears to be low, and such patients can be considered for the ileoanal procedure. This particular pattern of Crohn’s disease, however, is rare, as most patients with Crohn’s proctocolitis will have some degree of small bowel involvement or perineal manifestations and thus would not be considered candidates for the ileoanal procedure.
PROCTITIS

Crohn’s inflammation limited to the rectum is unusual. Surgical management of Crohn’s proctitis mandates proctectomy with permanent stoma. The need for resection of the normal proximal colon is controversial. Abdominoperineal resection with end sigmoid colostomy has been associated in some reports with a high risk for stomal complications and recurrent disease in the proximal intestine when compared to total proctocolectomy with end ileostomy. For these reasons, total proctocolectomy with ileostomy has been recommended for Crohn’s disease limited to the rectum and distal colon. This more extensive resection may be of greater value in younger patients who have no history of small bowel Crohn’s disease, as it appears that colorectal Crohn’s disease without small bowel involvement is unlikely to result in recurrence within the small bowel once a proctocolectomy is performed.43 If the patient has undergone a prior resection for small bowel Crohn’s disease, they may be at risk for high output from the ileostomy and therefore may benefit from the preservation of colonic absorptive capacity. Preservation of the colonic absorptive capacity may be beneficial also in the elderly patient. Thus, these patients may be better managed with a proctectomy and end sigmoid colostomy.

Proctectomy for Crohn’s disease does not require a wide excision of perirectal tissue. To avoid injury to pelvic sympathetic and parasympathetic nerves, the dissection should be undertaken close to the rectal wall. This is sometimes challenging in the presence of severe rectal mesenteric inflammatory reaction. In the absence of significant perianal disease, the perineal dissection is best carried out along the plane between the internal and external sphincters.179 This intersphincteric dissection allows for a perineal closure that is associated with fewer complications and better healing than wider dissections that encompass the entire sphincter mechanism. In some patients, fistula from the perianal Crohn’s disease can traverse the intersphincteric plane and a wider dissection is required in order to encompass the diseased tissue. In the presence of significant perianal disease, a staged approach, as described previously, can be used as an option. Occasionally, however, because of extensive rectal disease, closure of the rectal stump may be technically challenging or not feasible, forcing the surgeon to proceed with a proctectomy in the face of perianal sepsis. These dissections may need to be carried out widely, and extensive loss of perianal
skin and subcutaneous tissue may occur. The resultant defects are often too large for primary closure, and closure may require advanced tissue transfer techniques such as gluteal flaps, gracilis flaps, or myocutaneous rectus abdominis pedicle flaps. These closures may have to be staged as well in the presence of perineal sepsis. Large open perineal wounds may be managed temporarily or definitively with the assistance of the vacuum-assisted closure device. This device allows for rapid contracture of the wound and facilitates healing.

**SEGMENTAL COLITIS**

The optimal management of segmental colitis is dependent primarily on the location of the disease and secondarily on the presence and severity of concurrent perineal complications, the degree of fecal continence, and the natural history of the disease in the residual colon. Segmental involvement of the right colon should be managed by simple right hemicolecctiony with ileotransverse anastomosis. For segmental disease involving the transverse colon, an extended right hemicolecctiony is generally preferred to a segmental transverse colectomy. Such an approach may have a lower risk of recurrence compared to a segmental resection of the transverse colon. In addition, the extended right hemicolecctiony avoids a colocolonic anastomosis that is associated with a higher risk for anastomotic dehiscences and strictures.

For disease in the descending or sigmoid colon, the appropriate surgery is more controversial. Presence and severity of concurrent perineal complications, the degree of fecal continence, and the natural history of the disease in the residual colon all play a role in deciding on the approach for each individual patient. Studies have indicated that segmental colonic resection with colocolonic anastomosis or rarely colonic strictureplasty can be performed with overall good results. However, such a strategy may be at risk for early disease recurrence within the colon. Even if the risk for recurrence is higher with segmental resection, the benefits of preserving the absorptive capacity in appropriately selected cases may outweigh the higher risk of recurrence.

**PERIANAL DISEASE**

The perianal manifestations of Crohn’s disease include abscesses, fistulas,
fissures, anal stenosis, and hypertrophic skin tags.\textsuperscript{182,183} Perianal Crohn’s disease originates from inflammation within the anal crypts. This inflammation gives rise to sepsis and to fistulization (Fig. 45-20). Perianal Crohn’s disease is common and occurs in one-third of the patients who suffer from intestinal Crohn’s disease.\textsuperscript{45} Perianal Crohn’s disease is usually associated with active or quiescent disease elsewhere within the GI tract. It is controversial as to whether the activity of perianal Crohn’s disease parallels that of the intestinal disease. There is also controversy over whether medical or surgical control of the intestinal disease can ameliorate the perianal manifestations. Unlike idiopathic perianal abscesses and fistula-in-ano that occur in patients without Crohn’s disease, perianal Crohn’s disease tends to be recurrent, complex, and sometimes progressive.

\textbf{FIGURE 45-20} Dynamic proctogram demonstrating Crohn’s fistula-in-ano. (Reproduced with permission from the University of Chicago General Surgery Archives.)
Surgical incision and drainage are required to manage perianal abscesses (Fig. 45-21). Attempts at treating purulent collections with antibiotics alone are invariably unsuccessful. With surgical drainage of the abscess, the incision should be placed close to the anal margin. The cavity may be packed with ribbon gauze or drained with a 10- to 16-Fr mushroom catheter. If a fistula tract can be identified at the time of drainage of the suppuration, a loose seton may be placed to ensure adequate drainage.

**FIGURE 45-21** CT scan demonstrating a large perirectal abscess secondary to Crohn’s disease. (Reproduced with permission from the University of Chicago General Surgery Archives.)

Uncomplicated submucosal or intersphincteric fistulas are best treated with an initial trial of either metronidazole or ciprofloxacin. These antibiotics are moderately effective in promoting healing of Crohn’s fistulas and are associated with a low risk of complication.\textsuperscript{184,185} If a low-lying submucosal or intersphincteric fistula fails to heal with antibiotic treatment, a surgical fistulotomy can be performed. These low-lying fistulas typically heal well after fistulotomy, and the risk of incontinence is low.

Surgical fistulotomies and cutting setons should not be used for suprasphincteric fistulas and should also be avoided for most transsphincteric
fistulas. For complex fistulas, the risk for surgical complications is higher, and more aggressive medical therapy is warranted before surgery is recommended. Medical treatment for extensive Crohn’s fistulas includes the use of 6-MP, azathioprine, and cyclosporine. Probably the most effective agent at promoting healing of perianal fistulas related to Crohn’s disease is infliximab. With infliximab treatment, healing of complex perianal fistulas is seen in 60% of cases.\textsuperscript{186,187} Recurrence of the fistula after infliximab is discontinued, however, may be high. Additionally, persistent stasis or sepsis within the fistula tract can impede effective healing with medical treatment. To provide for adequate drainage throughout the fistula tract, many patients may benefit from placement of setons. The use of setons with infliximab therapy can improve the overall effectiveness of infliximab.\textsuperscript{188} Typically the seton is placed prior to the initiation of infliximab therapy and then is removed after the second or third dose.

Fibrin glue has been used for the treatment of Crohn’s disease–related fistulas, but reported experience is limited. Success rates with this approach are low, but given the low risk of complications, an attempt at fibrin glue may be worthwhile in selected cases.\textsuperscript{189,190}

Closure of the internal opening of the fistula with a rectal advancement flap can be considered in cases of Crohn’s disease.\textsuperscript{191} With this approach, an incision is made at the dentate line, and a flap of mucosa and muscularis is undermined and advanced down over the internal opening of the fistula. The advancement flap is then sutured into position with absorbable sutures. Rectal advancement flaps for Crohn’s disease have a low risk for anal incontinence but are associated with a high failure rate. Rectal advancement flaps are not appropriate in patients in whom the rectal mucosa is involved with Crohn’s disease. In severe cases of perianal disease that do not respond to aggressive medical and surgical therapy, fecal diversion with a stoma may be necessary. Diversion of the fecal stream typically results in significant relief of local inflammation and can assist in the healing of perianal fistulas. Proctectomy is indicated when perianal disease is unrelenting or when damage to the sphincters results in debilitating incontinence.

**POSTOPERATIVE RECURRENT DISEASE**

Crohn’s disease carries a high risk for recurrence after surgery. The actual
incidence of recurrent disease depends on the defining parameters of recurrence. For example, histologic evidence for recurrence can be seen in many patients within days of surgical resection. Endoscopic evidence for recurrent Crohn’s disease can be seen in over 80% of patients within 3 years. Most cases of histologic or endoscopically detected recurrences, however, do not go on to produce symptoms of Crohn’s disease. For this reason, histologic or endoscopic evidence of recurrent disease may be used as an end point in investigative studies but is not typically used as a guide for clinical management.

The development of symptoms related to recurrent Crohn’s disease activity is the most commonly applied definition of disease recurrence, as it is the recurrence of symptoms that has the most relevance to the patient. The onset of symptoms of recurrent Crohn’s disease is often insidious, and the severity of symptoms varies greatly. To create a reproducible standard for recurrence of Crohn’s disease symptoms, the Crohn’s Disease Activity Index (CDAI) can be applied as a means of measuring recurrent disease. A CDAI of greater than 150 is generally accepted as defining clinical recurrence. Once symptoms suggestive of recurrent disease occur, it is still necessary to carry out radiologic and endoscopic tests to confirm that the symptoms are in fact related to Crohn’s disease.

The clearest end point as a definition of recurrence is the need for reoperation. Dates of surgery are readily documented even in a retrospective fashion. While reoperation is the most precise definition of recurrence, even this standard does not allow for accurate and reproducible comparisons between series as some centers may submit patients to surgery earlier than other centers.

Reported crude and cumulative recurrence rates vary greatly. Symptomatic or clinical recurrence occurs in about 60% of patients at 5 years, and recurrences increase with time such that at 20 years clinical recurrence can occur in between 75% and 95% of cases. Reports of surgical recurrence rates range from 10% to 30% at 5 years, 20% to 45% at 10 years, and 50% to 70% at 20 years.

While many factors that may influence the risk of recurrence have been studied, the cumulative literature has validated very few as true risk factors. The data are conflicting for most of the proposed predictors of recurrent Crohn’s disease. Much of the clinical data examining potential risk factors
are confounded by poorly defined end points and improper study design. There is, however, general consensus that cigarette smoking has a significant effect on the clinical course of Crohn’s disease.\textsuperscript{30} Smoking not only exacerbates existing Crohn’s disease but also has been identified as a risk factor for the development of recurrent Crohn’s.\textsuperscript{27,28,30} What is so striking about the effect of cigarettes on Crohn’s disease is that smoking has the opposite effect on what is thought to be a very similar disease, ulcerative colitis.\textsuperscript{29} While smoking exacerbates Crohn’s disease, it seems to lessen the activity of ulcerative colitis.

The mechanism by which smoking results in exacerbation of Crohn’s disease is not known. Smoking is an independent risk factor for endoscopic, symptomatic, and surgical recurrence.\textsuperscript{31,32} The risk from smoking appears to be dose-related, with heavy smokers being at higher risk. This effect is reversible, as smokers who quit smoking prior to surgery can lower their risk of recurrence to a level similar to that of nonsmokers. Because of the harmful effects on the clinical course of Crohn’s disease combined with the many other clearly established health hazards caused by cigarette smoking, all patients with Crohn’s disease should be strongly counseled to quit smoking.

There is concern that NSAIDs may exacerbate the activity of both ulcerative colitis and Crohn’s disease.\textsuperscript{74,82} Although there are no studies that have examined the specific issue of NSAIDs and the risks for postoperative recurrence of Crohn’s disease, the currently available data certainly warrant some caution, and patients with Crohn’s disease should be advised to avoid NSAIDs.

**POSTOPERATIVE PREVENTION AND MAINTENANCE THERAPY**

**Medical Prevention/Maintenance**

The risk for recurrent disease can be lessened with postoperative maintenance therapy. Traditionally the most common agents used for postoperative suppression of disease were controlled-release 5-ASA (Pentasa) and 6-MP.\textsuperscript{77-79} Maintenance with 5-ASA is associated with few side effects, but up to 16 pills have to be taken daily. 6-MP is less expensive and is taken on a once-
daily basis. Additionally, 6-MP may be more effective in diminishing the risk of recurrence.\textsuperscript{77} 6-MP, however, is associated with potential bone marrow suppression, so that patients on 6-MP maintenance must be followed with periodic blood cell counts. The effect of these agents on the natural course of Crohn’s disease is not dramatic, and many patients will go on to develop recurrence while on maintenance therapy. The largest benefit demonstrated with 6-MP in a multicenter trial showed a decrease of symptomatic recurrence from 77\% with placebo to 50\% with 6-MP.\textsuperscript{77} Recently, anti-TNF agents have shown efficacy in the prevention of Crohn’s disease after resection. Most studies of anti-TNF agents have focused on 1-year clinical and endoscopic outcomes. A more recent randomized controlled trial by Regueiro et al\textsuperscript{202} followed patients for 5 years after their initial surgery and showed a decreased recurrence rate and longer time to recurrence in patients being treated with anti-TNF medications. The options for maintenance therapy should be considered for most patients with Crohn’s after operative intervention, but the decision for such therapy must be individualized for each patient.\textsuperscript{203-205}

**Surgical Prevention**

Recurrent Crohn’s disease is most likely to occur in proximity to the location of the previously resected intestinal segment, typically at the anastomosis and preanastomotic bowel.\textsuperscript{100} This is particularly true for terminal ileal disease. Additionally, the length of small bowel involved with recurrent disease parallels the length of disease originally resected.\textsuperscript{206,207} Short-segment disease tends to recur over a short segment of the preanastomotic bowel, and lengthy disease typically is followed by lengthy recurrence. In addition, stenotic disease tends to recur as stenotic disease, and perforating disease tends to recur as perforating disease.\textsuperscript{197}

There are mixed data on the role of surgical technique and procedure type in minimizing postoperative recurrence. Guo et al\textsuperscript{208} performed a meta-analysis in 2013 evaluating side-to-side anastomoses in comparison to hand-sewn end-to-end anastomoses for small bowel disease and were unable to demonstrate a reduction in postoperative recurrence with side-to-side anastomoses. The difference between a side-to-side or end-to-end anastomosis for an ileocolic resection was evaluated by Mcleod et al\textsuperscript{209} in a
randomized controlled trial, and no difference was found between the 2 anastomotic types. Interestingly, however, Yamamoto et al.\textsuperscript{210} had previously demonstrated that in patients who underwent strictureplasty at a diseased segment there seemed to be a protective effect of the strictureplasty as these patients have lower recurrence than those undergoing segmental resection. More recently, Japanese surgeon Toru Kono has described a new antimesenteric functional end-to-end hand-sewn anastomosis (Kono-S) (Fig. 45-22). Initial results from this author have been very encouraging, showing lower rates of recurrence compared to historical controls (0\% vs 15\%; $P = 0.0013$) at 5 years. A multicenter randomized trial is under way in the United States to evaluate the Kono-S anastomosis compared with a standard anastomosis.\textsuperscript{211}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Kono-S_anastomosis.png}
\caption{Antimesenteric functional end-to-end hand-sewn (Kono-S) anastomosis.}
\end{figure}
The Kono-S anastomosis is performed by first identifying and mobilizing the segment of bowel to be resected. Control of the lumen of the bowel proximal and distal to the disease segment is obtained by firing a linear GIA stapler with 4.8 staples placed perpendicular to the mesentery. The intervening mesentery is divided very close to the bowel to preserve innervation and vascularization. The GI continuity is then reestablished with a side-to-side antimesenteric enteroenteric anastomosis. Specifically, the 2 stapled suture lines are brought together with interrupted 3-0 silk sutures to serve as a support structure for the anastomosis. A 7- to 8-cm enterotomy is then created, starting 0.7 cm proximal to the stapled suture line on the antimesenteric side of the afferent intestinal loop in a distal to proximal direction; a similar length enterotomy is then created on the antimesenteric portion of the efferent intestinal loop, starting at 0.7 cm from the stapled suture line in a proximal-to-distal direction. The anastomosis is then performed in a side-to-side transverse direction between the 2 enterotomies with an internal layer of running 3-0 Vicryl. The anastomosis is then reinforced with an outer layer of interrupted 3-0 silk Lembert stitches. While preliminary results of the Kono-S are encouraging, the debate over surgical and anastomotic technique in Crohn’s is far from over, and more research is needed.

CONCLUSIONS

Management of Crohn’s disease is complex and requires a multidisciplinary team approach. Diagnosis involves a focus on patient clinical exam, supplemented by radiology and confirmed by pathology. Initial management is typically medical and has had several advances over the past few years. Surgical intervention is typically reserved for refractory disease or complications of the disease and should be managed by surgeons with significant clinical expertise in inflammatory bowel disease working closely with their GI colleagues. While significant progress has been made over the past 30 years and new medications are changing the course of treatment, much more work remains to be done, including understanding how these medications will shift surgical treatment and whether specific surgical techniques lower the risk of recurrent disease.
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INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing and remitting intestinal disorder plagued by diffuse and continuous mucosal inflammation involving the rectum, and extending proximally throughout the colon. As one of two well-known disease types grouped under the umbrella of inflammatory bowel diseases (IBDs), the inflammatory hallmark in UC is limited to the mucosa. The etiology of UC is not yet completely understood; however, research over the last several decades has led to a better understanding of cellular, immunological, and molecular mechanisms involved in its pathogenesis. Scientists continue to discover new and innovative approaches in the development of potential biomarkers, diagnostic tools, and treatment options for patients with this disease. In this chapter, the authors present a broad overview of disease epidemiology, presentation and diagnosis, and current options for medical management with a focus on the surgical approaches to treatment of UC.
EPIDEMIOLOGY

Over 1.5 million Americans and 2.2 million Europeans are currently estimated to be afflicted with UC.\(^1\) The incidence of UC in the United States and Northern Europe is 9 to 20 cases per 100,000 patients per year.\(^2\) Its prevalence ranges from 156 to 291 cases per 100,000 people.\(^2\) UC is less common in Eastern and Southern European countries, specifically among Asian, Hispanic, and African American populations. Ashkenazi Jews have demonstrated some of the highest frequencies of UC, estimated at 3 to 5 times higher than other ethnic groups.\(^2\) No significant gender discrepancy has been documented. Disease onset is not targeted to a specific age group and may present at any time. However, the age of onset is bimodal in distribution, wherein the primary peak is typically 15 to 30 years and a second, smaller peak occurs in the sixth to seventh decade of life.

PATHOPHYSIOLOGY

Although the exact pathophysiology of UC remains unknown, it is postulated to be the result of a combination of dysregulated interactions between the host’s genetic predisposition, environmental triggers and exposures, and the intestinal microbiome, all of which undoubtedly interact with the innate and adaptive immune systems. The overarching hypotheses suggest that the above-mentioned factors function dependently on one another to establish and maintain intestinal homeostasis, which is altered upon dysregulation of any of the contributing players, presenting a platform upon which UC can develop.

Studies in molecular genetics have shed light onto the genetic contribution to the development of UC. Monozygotic twin studies have demonstrated concordance rates of 16% in UC.\(^3\) In addition, 8% to 14% of patients with UC were found with a family history of IBD, and a first-degree family member with UC statistically increases a person’s risk of development of IBD by approximately tenfold.\(^3,4\) To date, genome-wide association studies have identified 163 loci linked to IBD.\(^3\) Although disease-specific genes have not yet been identified, patients with UC are often found with mutations of epithelial barrier function, innate and adaptive immune responses, and response to oxidative stress.
Over the years, it has become clear that the environment plays a pivotal role in the onset and progression of UC. This was first evidenced by epidemiological studies demonstrating an increased incidence of disease from 5.3 to 10 per 100,000 people in second-generation Asian immigrants to the United Kingdom. Many modifiable risk factors have been identified in the literature. Western diets high in saturated fats, refined sugars, meats, and milk products are linked to increased risk of developing UC. In contrast to Crohn’s disease, smoking has been found to have a protective effect in UC. Smokers are less likely to develop UC and milder disease. Breastfeeding has also shown protective effects against UC if continued for greater than 3 months. Some evidence suggests that lifestyle factors such as high stress, poor sleep habits, and decreased exercise can be risk factors for development of UC. Finally, studies have demonstrated patients who have undergone an appendectomy are at decreased risk of developing UC, although the mechanism of this protective effect is not fully understood.

Alterations in the gut microbiome have been implicated in the development of UC, generating a greater emphasis in research to understand this complex interaction. To illustrate this, an infection with Salmonella or Campylobacter has been associated with an 8- to 10-fold increased risk of developing of UC the following year. Likewise, use of certain medications, such as NSAIDs and antibiotics, which can alter the gut microflora, is linked to an increased risk of IBD development.

**DIAGNOSIS**

The diagnosis of UC is established through a combination of clinical presentation, laboratory tests, imaging, and endoscopic evaluation. A universal scoring or classification system has yet to be widely accepted. Several parameters have been described, such as disease severity (mild, moderate, severe, or fulminant), age of onset, and extent of disease (proctitis, proctosigmoiditis, left-sided, or pan-colitis). All other forms of colitis including infectious, ischemic, and radiation colitis should be excluded prior to diagnosis of UC in a patient.

Typically, patients will present with complaints of hematochezia, abdominal pain, diarrhea, pain with defecation, occult or gross rectal bleeding, and/or tenesmus. Symptoms gradually progress over the course of
several weeks to months. Eventually, the patient may develop systemic symptoms including low-grade temperatures, weight loss, and fatigue.

There are no disease-specific laboratory tests to diagnose UC. Nonspecific markers of inflammation are often measured, including elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), iron-deficiency anemia (in the instance of chronic rectal bleeding), thrombocytosis, and hypoalbuminemia. In addition, fecal calprotectin (FC) or stool lactoferrin (SL) is more sensitive (88% for FC, 82% for SL) and specific (79% for FC, 79% for SL) markers of intestinal inflammation, although these biomarkers are also elevated in intestinal inflammation of any etiology. Autoantibodies may be helpful in differentiating Crohn’s disease from UC. Antineutrophil-cytoplasmic antibodies (ANCA), specifically perinuclear antibodies (pANCA), are found in approximately 60% to 70% of patients with UC, compared to 2% to 28% of patients with Crohn’s. In contrast, anti-\textit{Saccharomyces cerevisiae} antibodies (ASCA) are found in 39% to 69% of Crohn’s patients but only 5% to 15% of UC patients. Other antibody testing including anti-goblet cell antibodies (GAB) can be used to differentiate UC patients from other forms of colitis.

Imaging serves as a useful adjunct to diagnosis since it may demonstrate direct evidence of colonic inflammation. Modalities such as computed tomography, ultrasound, MRI, and endoscopy (Figs 46-1, 46-2, and 46-3) can reveal acute mucosal wall thickening, fat stranding, and perforation. Leukocyte scintigraphy is an uncommon imaging technique used to quantify leukocytes in the intestinal wall. It is particularly useful in ascertaining the distribution (continuous vs discontinuous) of disease and response to treatment. However, endoscopy remains the gold standard for imaging in the diagnosis of UC.
FIGURE 46-1 MRI. Yellow arrows point to segments of visualized colon which are narrowed, ahastral, and foreshortened.
FIGURE 46-2  CT. This is a representation of the classic lead pipe in both descending and ascending colon (yellow arrows). This effect is less appreciated on the right. The thick red arrow demonstrates post-inflammatory polyps, which are true reparative lesions as opposed to pseudopolyps.
FIGURE 46-3 CT, Pancolitis. A. This cross-section clearly demonstrates pancolitis with a striated wall appearance from mucosal enhancement and
intramural edema (yellow arrows). B. This is a patient with an acute on chronic UC flare. The striated appearance is due to chronic submucosal fat deposition.

All patients with presumed UC should undergo both an esophagogastroduodenoscopy (EGD) and colonoscopy with sampling of the ileum, four colonic sites, and the rectum, with a minimum of two biopsies from each site. Typically, the bowel of patients with UC demonstrates diffuse continuous mucosal inflammation, characterized by edema and widespread erythema with ulcerations and bleeding starting at the rectum with proximal extension (Fig. 46-4). In addition, there is often loss of vascularity, loss of haustral folds, mucosal erosions, mucosal friability, and evidence of mucopurulent exudates. Pseudopolyps are often observed in longstanding disease. Histologically, the mucosa is infiltrated with inflammatory cells; namely, mononuclear cells with plasmacytosis and lymphocytes, villous atrophy, goblet cell depletion, crypt cell branching and atrophy, Paneth cell metaplasia, and crypt cell abscesses.
**FIGURE 46-4** An endoscopic view of ulcerative colitis. A. Mild ulcerative colitis. B. Moderate ulcerative colitis. C. Severe ulcerative colitis. The mucosa is plagued with white exudative granularities.

**MEDICAL MANAGEMENT**

UC is a chronic medical condition that is not medically curable, but like other chronic health conditions it requires long-term therapy directed at controlling gastrointestinal inflammation. The two main goals of medical treatment for
UC are achieving clinical remission (the absence of symptoms), and once that is accomplished, maintaining remission (prevention of flare-ups). To achieve the goals of therapy, two treatment strategies are used: induction and maintenance therapy.

Induction therapy is defined as a treatment that induces a quick treatment response and achieves clinical remission. The initial choice of therapy depends upon the severity of disease and required rapidity of action. For example, a patient who feels well but has a high disease burden may be able to wait the necessary 3 or 4 months for immunomodulators to take effect, whereas a patient who is significantly symptomatic needs an effective agent with immediate action. Maintenance therapy is defined as a treatment that has been proven in clinical studies to prevent relapses and maintains patients in clinical remission. These medications have different onsets of action, and the choice of therapy depends on the severity of disease. Medications that are used as maintenance therapy are called corticosteroid-sparing therapy. Corticosteroids are not effective in the prevention of flare-ups and have many undesirable side effects so are not used as maintenance therapy.

Most patients will be managed with medical therapy and kept in clinical remission, as only 10% to 15% of patients will require surgical therapy. Surgical management is reserved for patients with severe colitis with or without complications (eg, toxic megacolon), or those with chronic colitis unresponsive to maximal medical management. Prior to proceeding with surgical treatment, consultation with a gastroenterologist should be considered to evaluate that maximal medical therapy has been used and to exclude conditions that may exacerbate disease (eg, Clostridium difficile colitis). In the following sections we review the medical management for outpatient and hospitalized patients with UC.

OUTPATIENT MEDICAL THERAPY

Aminosalicylates

Aminosalicylates are commonly used to treat mild to moderate UC and can be administered orally or topically. Sulfasalazine consists of an antibacterial component, sulfapyridine, bonded by an azo-bond to a salicylate, 5-aminosalicylic acid (5-ASA [mesalamine]). Sulfasalazine is split by bacteria
into active components in the colon. The mesalamine portion is the active portion of the drug and acts by interruption of the lipoxygenase and cyclooxygenase pathways, decreased production of IL-1, IL-2, and tumor necrosis factor (TNF) in the colonic mucosa. 5-ASA has been found to be effective in inducing and maintaining clinical remission in mild to moderate UC and usually improves symptoms by 2 to 4 weeks. Agents with 5-ASA are generally well tolerated, unlike sulfasalazine, in which patients usually experience side effects from the sulfa component. Rarely, 5-ASA can cause a paradoxical reaction leading to worsening diarrhea and should be stopped.

**Thiopurines**

Thiopurines (azathioprine and mercaptopurine) are immunomodulators that downregulate the activity of the immune system, and in turn decrease the gastrointestinal inflammatory response. Azathiopurine and 6-mercaptopurine are inactive prodrugs that require enzymatic conversion to produce active metabolites. These are purine analogs that become incorporated into DNA and inhibit DNA synthesis. They interfere with nucleic acid metabolism and cell growth and exert cytotoxic effects on lymphoid cells. The main limitation of these medications is their slow onset of action, which can be from 2 to 6 months and therefore this is not an effective medication to induce remission. However, they are effective in maintaining clinical remission in moderate to severe UC. A meta-analysis showed that compared to placebo, only five patients needed to be treated to maintain remission.\(^\text{11}\) Thiopurines are generally well tolerated, but side effects include reversible bone marrow suppression, increased liver function test, pancreatitis, and opportunistic infections.

**Biologics**

Biologics are genetically engineered medications that interfere with the body’s inflammatory response in IBD by targeting specific molecular players in the process such as TNF. Unlike corticosteroids, which tend to suppress the entire immune system and thereby have the potential to produce major systemic side effects, biologics offer a distinct advantage in IBD treatment because they act selectively, with a targeted mechanism of action.
TNF INHIBITORS

Infliximab, adalilumab, and golilumab are effective in inducing and maintaining clinical remission in UC.\(^{12-15}\) Infliximab is a chimeric anti-TNF inhibitor and is administered intravenously every 8 weeks after induction dosing. Adalilumab and golilumab are fully humanized anti-TNF inhibitors and are administered by subcutaneous injection every 2 weeks or monthly, respectively. These drugs work by binding to and preventing the activity of a specific protein in the body, tumor necrosis factor-alpha (TNF-\(\alpha\)). TNF-\(\alpha\) is a cytokine, a specialized protein that promotes inflammation in the intestine and other organs and tissues. The agent binds to soluble and membrane-bound TNF-\(\alpha\), deactivating it and resulting in reduced inflammation. Use of thiopurines in combination with infliximab was found to be more efficacious in maintaining clinical remission compared to infliximab alone.\(^{16}\) TNF inhibitors can exacerbate latent tuberculosis or hepatitis B, leading to disseminated tuberculosis or fulminant hepatitis B. Therefore, prior to initiating TNF inhibitors patients should be evaluated for these infections. Patients who are using TNF inhibitors also carry an increased risk for opportunistic infections, lymphoma, and non-melanoma skin cancer.

SELECTIVE ADHESION MOLECULE INHIBITORS

Vedolizumab is the first selective adhesion molecule inhibitor, and was approved in May 2014. It is a humanized monoclonal antibody that inhibits adhesion molecule \(\alpha4\beta7\), which results in blocking leukocyte migration and therefore gut inflammation. It only targets gastrointestinal leukocyte migration and provides selective immunosuppression of the gastrointestinal tract and does not cause systemic immunosuppression like TNF inhibitors. The GEMINI trial found it to be effective in inducing and maintain remission in moderate to severe UC.\(^{17}\) There do not appear any increased risks of adverse events or infections with vedolizumab.

Corticosteroids

Corticosteroids are potent nonspecific mediators of the inflammatory response. They can be administered by mouth, intravenously, or by rectum. They are effective in induction therapy but are not effective in maintaining
remission. Corticosteroids decrease inflammation by inhibiting arachidonic acid and cytokine release, and by inhibiting chemotaxis and phagocytosis. Corticosteroids are associated with many significant side effects (eg, osteoporosis, diabetes, cataracts, infections) and should always be used in conjunction with corticosteroid sparing therapy.

**INPATIENT MANAGEMENT**

Patients failing outpatient medical management should be admitted for intravenous corticosteroids, which are essential in the management of severe or fulminant UC; up to 70% of patients will respond to intravenous corticosteroids. Patients admitted for acute management of UC should receive 400 mg of hydrocortisone per day or 60 mg of methylprednisolone in divided doses. The medication should be administered in bolus injections, since they were no more effective than continuous infusion.

While awaiting a response to corticosteroids, a flexible sigmoidoscopy should be performed to confirm the degree of inflammation and exclude infections. *C. difficile* infections can increase risk for blood transfusion, surgery, and mortality in patients with UC. Cytomegalovirus infection can be associated with steroid refractory UC and excluded with colonic biopsies. All patients should receive thromboprophylaxis with subcutaneous heparin or low molecular weight heparin, since patients are at increased risk for deep venous thromboembolism. There is no evidence to suggest that empirical treatment with antibiotics in severe colitis is beneficial. Agents that could potentially precipitate the effects of toxic megacolon, such as anticholinergics, antidiarrheals, NSAIDs, and opiates, should be discontinued.

A response of corticosteroids should be seen by 3 to 5 days. If a response is not seen, rescue therapy with higher level medications or surgery should be strongly considered, as continuing steroids is unlikely to lead to a clinical benefit. Infliximab and cyclosporine have both been shown to be effective rescue therapy; a recent clinical trial demonstrated both to have similar efficacy in inducing clinical remission and preventing colectomy. Infliximab is more commonly used due to its better safety profile compared to cyclosporine, which can have serious adverse effects including nephrotoxicity, seizures, and infections. Infliximab in the inpatient setting
can have long-term benefits, with colectomy rates of 50% 3 years after treatment.\textsuperscript{24}

**SURGICAL MANAGEMENT**

Despite the improvements made in medical therapy, the only definitive cure for UC remains surgical resection of the colon and rectum. As mentioned, the majority of patients can be managed adequately with medical treatment; however, when emergencies are included, as many as 45% of patients have been reported to require operative treatment.\textsuperscript{25,26} The overwhelming benefit is elimination of disease, countered by wide variability in function and re-establishing continence postoperatively. Despite these challenges, most patients report a high quality of life with satisfactory long-term functional outcomes.\textsuperscript{26}

**Indication for Surgical Intervention**

The overarching principle in surgical treatment is to eliminate disease and the risk of colorectal cancer. The main goals of operative intervention include achieving definitive cure by resection of the colon and rectum, reconstructing a route of elimination, and minimizing morbidity and improving quality of life. As with all procedures, risks and complications are true possibilities. Surgery should be considered a therapeutic alternative rather than a failure of medical therapy. Hence, discussions between the patient, gastroenterologist, and colorectal surgeon should be introduced early into the patient’s treatment time course.

Given the wide variability in clinical manifestation, disease behavior largely directs the indications for surgical intervention. The first, and invariably the most straightforward, indication includes life-threatening complications such as toxic megacolon, perforation, and uncontrolled hemorrhage. The emergent nature of this approach is associated with higher morbidity and a greater number of subsequent operations.\textsuperscript{27,28} A second category encompasses cancer-related indications such as proven high-grade dysplasia, multifocal low-grade dysplasia, strictures, or localized cancer. A diagnosis of cancer and dysplasia is an absolute indication for surgery (Fig. 46-5). Patients comprising the largest indication category include those with
chronic, continuous disease and developed unresponsiveness to medical therapy. These patients are largely steroid dependent, have developed adverse effects, and exhibit insufficient responses to other medical therapies.

FIGURE 46-5 Barium enema. A patient with severe ulcerative colitis and a cancerous lesion in the ascending colon shown by a long apple-core segment
There is no doubt that the degree of ineffectiveness of medical therapies will vary among patients. Therefore it is critical that conversations regarding when the expectation of medical therapies have not been met are introduced to the patient, along with the treatment offered by surgical intervention. Pending no emergencies, the decision to proceed with elective colectomy may be left to the well-informed patient.\textsuperscript{25}

Historically, non-resectional strategies were the mainstay of surgical approaches, comprising segmental resections for limited disease scattered throughout the colon. The following section discusses the surgical options under acute and elective clinical scenarios, as the management of either is indicatively unique.

**MANAGEMENT OF ACUTE COLITIS**

Severe acute colitis presents a potential surgical emergency. Under ideal circumstances, acute colitis may be initially treated with medical therapy and daily re-evaluation. The patient should be informed that colectomy is a very possible alternative in the instance that the colitis is refractory to medical treatment. Deterioration or failure of symptoms to resolve within the first 3 days triggers the need for urgent colectomy.\textsuperscript{26} The absolute indications for surgery are toxic megacolon, perforation, and severe, unremitting colorectal bleeding (Fig. 46-6).\textsuperscript{27}
FIGURE 46-6 Abdominal plain radiograph, toxic megacolon. Grossly dilated transverse colon with “thumbprinting” due to mucosal edema.

If treatment is initiated via medical therapy, the colorectal surgeon must be consulted for early evaluation and daily assessment in the instance of any deterioration during IV steroid therapy or rescue treatment. Response to medical therapy may be objectively monitored by stool frequency, CRP levels, and abdominal imaging.\textsuperscript{27} Colectomy is recommended by the
European Crohn’s and Colitis Organization (ECCO) guidelines if there is no improvement by days 4 to 7 following initiation of medical therapy under acute circumstances, or if the patient has been taking 20 mg of prednisolone or more daily for over 6 weeks.\textsuperscript{10}

The operation of choice in urgent and emergent situations is total abdominal colectomy (TAC) with end ileostomy, leaving the rectum in situ. This is commonly a staged procedure where the goal is to remove the diseased colon as quickly as possible without distorting anatomic planes. Hence the rectum is not resected until a subsequent procedure may be planned to allow the patient to recover from the initial insult and taper off immunosuppressive medications. Management of the rectal stump remains problematic and can be a source of postoperative complications if it opens up in the postoperative period. Some surgeons opt for high ligation of the rectum at the level of the promontory with transanal rectal drainage. The alternative includes creating a mucous fistula, where the clear advantage lies in the fact that no closed bowel is left within the abdomen. Traditionally, emergent operations are performed in an open approach; however, evidence from specialty centers has recently emerged suggesting laparoscopic subtotal colectomy is not only safe, but demonstrates improved short-term perioperative outcomes.\textsuperscript{29,30} While clearly adding some benefit to patients in the acute setting, laparoscopy should be undertaken in this setting only by an expert laparoscopist. The colon is often enlarged and quite friable, increasing the technical difficulty of the operation. In addition, laparoscopy is contraindicated in patients who are septic or who have experienced a perforation.

**Brief Operative Technique**

Following induction of general anesthesia with endotracheal intubation, the procedure is begun with the patient in standard Lloyd-Davis position. A urinary catheter is placed and a site demarcating the end ileostomy is made in either the right or left lower quadrant. In the standard open approach, a midline incision provides adequate access into the abdomen with the option of placing the stoma in either lower quadrant. Initial exploration of the abdominal cavity is performed. It is here that the surgeon takes note of tissue integrity and friability in addition to any evidence of disease to the terminal ileum, as this could be suggestive of Crohn’s disease. This is particularly
important in the acute setting, or in a patient with an otherwise unknown diagnosis of UC. The colon is fully mobilized from its peritoneal attachments and both flexures are freed using a combination of cautery and energy devices. The mesentery is ligated and division of the mesenteric vessels is performed. The terminal ileum is then divided immediately proximal to the ileocecal valve. In the total abdominal colectomy, the colon is divided at the level of the mid to distal sigmoid with preservation of the inferior mesenteric artery and superior rectal arteries. In addition to preserving the presacral planes, it is critically important to preserve the ileocolic artery in order to allow for later pouch reconstruction. Preservation of the ileocolic artery prevents foreshortening of the mesentery, which allows the future pouch to easily reach to the anal canal.

Management of the rectal stump is largely dependent on the severity of colitis at the time of operation, as well as the friability of the rectosigmoid. The options for handling the rectum include the Hartmann pouch, where a 30 Fr catheter is passed transanally and left in place for decompression, a mucus fistula, or closure of the rectal stump with exteriorization into the subcutaneous tissue. The mucus fistula presents the safest approach in handling the rectum in the instance that tissue is very friable. Closure of the rectum with exteriorization into the subcutaneous tissue has been reported, suggesting outcomes are associated with fewer pelvic septic complications and overall morbidity. Regardless of management approach, it is important to recognize that the rectal stump can be a source of postoperative peritonitis if the patient suffers a stump blowout.

MANAGEMENT OF CHRONIC COLITIS

Although patients with chronic colitis are in better overall condition than those with acute colitis, healing conditions remain far from ideal. Often, these patients have undergone long-term steroid therapy, which incurs a high risk of septic complications and conditions for poor anastomotic healing. For these reasons, a staged procedure is preferred to allow for reconstruction at a later time. With the benefit of added time, efforts should be made to optimize nutritional status and minimize steroid use.

In the following section, we discuss the options available for reconstruction. The best choice is not always obvious and is largely
dependent on patient circumstances of life, gender, occupation, age, and lifestyle. It is therefore critical that all options are discussed with the patient before a final decision is made, as it will drastically impact the patient’s quality of life.

**Laparoscopic versus Open Approaches**

Laparoscopic ileal pouch anal anastomosis (IPAA) was initially described in 1992. Although more recent evidence from several randomized controlled trials suggests elective laparoscopic colectomy fares better in short-term perioperative outcomes compared to the open approach, only a handful of centers have reported outcomes specifically in IBD.\(^{30,32}\) Comparative studies have concluded that laparoscopic IPAA is deemed feasible and a safe approach with significant improvement in perioperative complications.\(^{29,30,32-34}\) Few investigators have examined short-term outcomes and complications after laparoscopic IPAA, such as pouchitis and pouch dysfunctional incontinence, frequency, and sexual function, revealing little difference compared to the open approach.\(^{29,32,34}\) In a study comparing open to laparoscopic IPAA, Fajardo and colleagues did not demonstrate differences in short-term outcomes between groups. However, patients who underwent laparoscopic reconstruction demonstrated a shorter elapsed time to ileostomy closure.\(^{35}\) Currently, there is insufficient data to tout the claim that laparoscopic IPAA leads to faster recovery, as patients who undergo elective restorative proctocolectomy (RPC) are typically younger, healthier, and more motivated.

In this era of advancing surgical techniques, laparoscopic surgery has been shown to be a safe and feasible alternative to open surgery in IBD.\(^{29,33,36}\) The outcomes generally studied include operative duration, intraoperative blood loss, time to return of bowel function, length of postoperative stay, and overall pain scores. Studies claim that the laparoscopic approach boasts decreased postoperative narcotic requirements, blood loss, and hospital length of stay, and decreased operative times, although results are inconsistent.\(^{29,33,34,37}\) Other centers report additional reduction in the time to subsequent IPAA.\(^{33}\) This aspect of a laparoscopic approach is particularly difficult to draw conclusions about, considering that the factors that influence delay to IPAA in UC is likely confounded by surgeon comfort and
preference, individual complication rates, and postoperative recovery times. Randomized controlled trials comparing laparoscopic and open approaches have shown lower rates of superficial surgical site infection (SSI) and earlier return of bowel function. The majority of reported series describing laparoscopic RPC have utilized the stapled ileal J-pouch configuration. Less commonly, S-pouch techniques are employed. As Harms and colleagues have described, there is additional time required to creating an S- versus a J-pouch in surgery, contributing to the significant increase in intraoperative time to the procedure compared to the open approach. However, the added time provides little difference in the overall costs incurred in a laparoscopic approach, due to shorter hospital stays. The greatest advantage to laparoscopic-assisted procedures is improved cosmesis due to reduced incision size. In a Cochrane review by Ahmed and colleagues, various series and clinical trials identified higher cosmesis scores and greater patient preference for laparoscopic approach compared to open. As with any laparoscopic approach, conversion to open surgery remains an enduring possibility in each surgeon’s mind. Studies estimate conversion rates ranging widely from 0% to 8%.

To briefly summarize the laparoscopic technique, the procedure involves a completely laparoscopic, intracorporeal total colectomy followed by either open or laparoscopic proctectomy. In the instance of immediate reconstruction with an open proctectomy, an IPAA is performed with or without mucosectomy. Two initial 12-mm ports are placed in the suprapubic and supraumbilical positions, followed by placement of two 5-mm ports in both left and right sides, to assume a diamond configuration. The colon is mobilized in a lateral-to-medial fashion and the omentum is preserved during mobilization of the transverse colon. Few series report routine removal of the omentum, with the notion that preserving it may increase the risk of obstruction from adhesion formation; however, there is no clear evidence to support this. A bipolar cautery is used to divide the mesocolon, and simultaneous attention is paid to ligating the ileocolic vessels. Following this, colon extraction is accomplished via a 7- to 8-cm extension of the suprapublic incision. Proctectomy and pouch reconstruction are accomplished via placement of a wound retractor into the same extended incision. A handsewn or stapled IPAA is performed. A standard diverting ileostomy is placed in the left lower quadrant for fecal diversion.
Alternatively, the operation can be performed in a completely laparoscopic fashion. In this approach, the abdomen is accessed with three 5-mm trocars in the supraumbilical, suprapubic, and left lower quadrant. A 10/12-mm trocar is placed in the right lower quadrant, completing the diamond configuration. The abdominal colon is mobilized and the mesentery ligated beginning at the distal sigmoid colon, working around to the right side of the abdomen. The most common approach is a lateral-to-medial dissection. However, medial-to-lateral dissection of the entire colon can be performed and has been shown to be a very efficient approach. In this approach, the mesentery is divided first, followed by complete medicalization of the colon. Once the entire abdominal colon is free from all attachments, attention is turned to the pelvis. The pelvic dissection is carried out under laparoscopic visualization. The proctectomy can be performed as a total mesorectal excision or, in the absence of a concern for malignancy or dysplasia, the dissection can be performed by skeletonizing the rectum and dividing the mesorectum with an energy device. Regardless of technique, the dissection is taken down to the top of the anorectal ring, at which point the rectum is divided with a laparoscopic stapling device. This portion of the procedure can prove to be quite difficult, and great care must be taken to divide the rectum low enough to ensure all disease is removed. Once this is completed, the colon and rectum must be extracted. This can be accomplished through the previously identified ileostomy site or through a suprapubic incision. The authors most commonly extract through the ileostomy site. Once the specimen is extracted, the ileal pouch is created in the standard fashion. The anvil of the circular stapler is inserted into the lumen of the pouch per anus and anvil is wed to the stapler. The ileostomy is then created through the extraction site.

**Total Colectomy with Ileorectal Anastomosis**

In select circumstances, ileorectal anastomosis (IRA) is an appropriate surgical option. Such an indication might be in a patient with chronic quiescent disease with a dysplastic lesion in the right colon. Following standard colectomy, the rectum is left intact, obviating deep pelvic dissection and potential injury to pelvic nerves. The benefits are perceived in the context of less impact on sexual function and fertility, owing to younger patients who have not completed their desires for childbearing. IRA was initially plagued by poor functional results and persistent rectal inflammation; this, however,
has improved over the years. As previously discussed, the rectal remnant requires continued medical therapy and surveillance, as the risks of colitis and later cancer have not been eliminated.

The anastomosis is commonly created at the level of the sacral promontory, where the superior hemorrhoidal vessels are left intact. A stapled or handsewn anastomosis can be performed in an end-to-end or end-to-side fashion.

**Total Proctocolectomy with Ileal Pouch-Anal Anastomosis**

RPC with IPAA is the elective procedure of choice for UC. Total proctocolectomy (TPC) is carried out as described above. The terminal ileum is reconstructed to recreate a fecal reservoir in order to mimic anorectal continence after colectomy. This can be performed either as a single or staged procedure. Since its introduction in 1978, numerous studies have demonstrated low morbidity, high quality of life, patient satisfaction, and good functional outcomes. Many variations to the ileal pouch have been described, including the S, J, and W, with the most common being the J-pouch (Fig. 46-7).
In the J-pouch reconstruction, an adequate length of the ileocolic pedicle must be confirmed, and the distal ileum is used to construct the J-pouch. There is an inflow and outflow limb of the pouch creating the J-shape. These are typically anastomosed together using a linear stapler. The apex of the pouch is then anastomosed to the rectal cuff, which is performed with a circular stapler, but may also be handsewn to the anal verge.

**Ileal Pouch-Anal Anastomosis**

There are two principle techniques that are currently used in pouch reconstruction, the handsewn and stapled techniques. There are three variations to how this procedure may be performed, separated in terms of the number of stages. A single-stage procedure encompasses removal of the colon and rectum with pouch reconstruction without a diverting ileostomy. The two-stage procedure involves total proctocolectomy with pouch reconstruction and diverting ileostomy, followed by closure of the ileostomy at a later time. The three-stage procedure involves an initial subtotal colectomy, followed by a completion proctectomy and pouch reconstruction with diverting ileostomy, completed by closure of the ileostomy.
A three-stage procedure is preferred when a patient presents with suboptimal conditions such as poor nutritional status, high steroid requirements, and severe colitis. This permits healing between operations so as to optimize the patient’s subsequent preoperative state. The two-stage procedure is most commonly performed in elective scenarios.

**HANDSEWN ANASTOMOSIS WITH MUCOSECTOMY OF THE ANAL TRANSITION ZONE**

Mucosectomy with handsewn anastomosis has long been the technique of choice for IPAA, particularly prior to the introduction of surgical staplers. This technique is more time-consuming and is associated with postoperative functional complications such as incontinence and seepage secondary to manipulation of the anal canal and sphincter stretching. Mucosectomy removes the entire rectal mucosa as completely as possible. Although the stapled technique offers various advantages, several surgeons continue to opt for mucosectomy with handsewn anastomosis given the concern over the risk of ongoing inflammation or cancer developing in the rectal remnant. The difficulty with handsewn anastomoses is also perceived in obese patients, where the pouch may be under tension.

**DOUBLE-STAPLED TECHNIQUE WITHOUT MUCOSECTOMY**

The stapled technique has gained much favor as the standard technique for IPAA given good outcomes and ease of approach. A stapled anastomosis is less likely to result in functional problems, however; utilization of the stapler head is introduced transanally, requiring a 1- to 2-cm remnant of rectal cuff, termed the anal transition zone (ATZ), which poses a risk for future development of cuffitis or dysplasia.

**Brief Surgical Technique for IPAA**

It is essential to ensure adequate length of the mesentery to allow mobilization of the small bowel in construction of the pouch. This may be accomplished by ligating the ileocolic vessels as proximal to the level of the takeoff from the superior mesenteric artery (SMA). In the stapled
anastomosis, a transverse linear cutting stapler is used to staple off the rectum at the level of the levators, leaving 1 to 2 cm of rectal mucosa. Pouch reconstruction is initiated by ensuring complete mobilization of the small bowel. This involves taking down inter-loop adhesions and mobilization of the small bowel. A general rule of thumb to ensure adequate length for a stapled anastomosis involves ease with extending the mesentery to the level beyond the pubic symphysis.

Constructing a J-pouch involves creating two 15-cm limbs by folding the terminal ileum onto itself. A small enterotomy is created at the apex of the pouch on the antimesenteric side of the bowel. This serves to allow a linear stapler to pass through and create the J conformation of the pouch. Next, a purse-string suture is placed at the enterotomy, which will secure around the endoanal anvil stapler which is passed transanally. This creates the ileoanal anastomosis. The stapler is fired and removed, and inspected for both proximal and distal tissue donuts. A leak test is then performed, followed by creation of a diverting ileostomy. The ileostomy is often found in the right lower quadrant. Figure 46-8 shows an endoscopic view of a normal J-pouch demonstrating the inlet and the blind end of the ileum comprising the tip of the “J”.

![Figure 46-8](image_url)
In the handsewn anastomosis, a Lone Star retractor is placed in the patient’s perineum. A solution of dilute epinephrine is injected into the submucosa to gently separate the mucosa away from the underlying tissue planes. The mucosectomy is then performed with electrocautery or via sharp dissection using Metzenbaum scissors, beginning at the level of the dentate line. The pouch is then gently advanced into the pelvis and the anastomosis between the ileal pouch and dentate line can be created using interrupted absorbable suture.

**Total Colectomy or Proctocolectomy with End Ileostomy**

Permanent ileostomy may be a consideration for patients with contraindications to restorative surgery, tolerance, and preference, particular among the elderly. Management of the rectal remnant remains the most burdensome aspect when total abdominal colectomy and end ileostomy is definitive. The rectal stump requires surveillance, continuing to pose cancer risk and unpredictability in symptom control if the patient were to develop extensive proctitis. Patients may also struggle with societal pressures and insecurities with body image on a daily basis as a result of the ileostomy.

As a result of the rectal concerns, the vast majority of patients who opt for an end ileostomy as a definitive treatment of their UC should have a total proctocolectomy consisting of removing the abdominal colon in the standard fashion as well as removing the entire rectum via an abdominoperineal approach. This can be performed in the open or laparoscopic fashion. Regardless of approach, the colon is removed in the standard fashion followed by complete rectum and anus removal. Following ligation of the superior hemorrhoidal vessels and inferior mesenteric vessels, the plane between the presacral fascia posterior to the rectum and fascia propria of the rectum is entered. Dissection of the pelvic floor is initiated posteriorly, progressing laterally and lastly, anteriorly. Throughout the dissection, care is taken not to injure the left ureter and sympathetic nerves. The rectum is skeletonized from the mesorectum to reduce the risk of parasympathetic nerve injury. Anteriorly, the dissection is carried out as closely to the
specimen as possible, on the rectal side of Denonvilliers’ fascia, also in avoidance of potential injuries to neighboring structures.

Upon completion of the abdominal and pelvic portion of the operations, the surgeon moves to the perineum. Assuming that there is no concern for cancer, an intersphincteric dissection of the anal canal can be performed to maintain pelvic muscular support of the perineal wound closure. In this technique, an incision is made around the anal canal and the intersphincteric space is entered circumferentially. The dissection is taken into the pelvis posteriorly and carried around both sides until the anus is completely free of all attachments in the perineum. The rectal specimen can then be extracted through the perineum. An intersphincteric resection enhances closure of the pelvic floor allowing closure of the healthy muscle. This theoretically decreases wound complications in the short and long term.

**Kock Pouch**

A continent ileostomy was first described by Kock in 1969. It was described as a high-volume, low-pressure reservoir maintained by an intussuscepted nipple valve (Fig. 46-9). The design of the pouch was to permit fecal material to accumulate and be emptied at the patient’s convenience several times a day. This was accomplished by inserting a tube at the level of the stoma into the reservoir to release its contents. Although the concept proved promising, it was idealistic at best given Kock pouches failed to achieve high levels of acceptance due to frequent complications. Currently, the Kock pouch serves as a surgical rescue option following failed IPAA or for those who are not deemed appropriate IPAA candidates. Major complications include valve dysfunction, the most common of which is valve de-intussusception.
FIGURE 46-9  Kock pouch. A high volume, low-pressure reservoir maintained by an intussuscepted nipple valve. This design permits fecal material to accumulate and be emptied at the patient’s convenience several times a day. This is accomplished by inserting a tube at the level of the stoma into the reservoir to release its contents.

POSTOPERATIVE COMPLICATIONS

Pouch-related complications are categorized broadly into those with septic and non-septic sequelae. Septic complications are those characterized by infections originating in the pouch which consequently spread to the pelvic space, and include anastomotic leak, abscess, and fistulas. Non-septic complications present a slightly larger repertoire of clinical events that arise over a longer postoperative time frame. These include obstructions, stricture, cuffitis, and pouchitis. Not uncommonly, septic-related complications present at earlier time courses; however, the majority of early complications are often attributed to predisposing patient factors such as local and general inflammatory changes, hypoalbuminemia, anemia, and prolonged steroid use.46

The J-pouch is created with two ridges corresponding to the anastomosis, creating a posterior appendage called the “J-pouch appendage.” The
appendage consists of the distalmost segment of the terminal ileum that is not incorporated into the reservoir. The length of the appendage is 1 to 2 cm and may potentially dilate over time, lending to downstream complications.

Lastly, the definition of pouch failure varies between series and authors. It is often referred to as either the need to remove the pouch and establish a permanent ileostomy or the need for an ileostomy without the anticipation of future closure. Here, we discuss an overview of the most commonly encountered immediate and later-stage postoperative complications along with current management strategies.

## Immediate Complications

### ANASTOMOTIC LEAK

Anastomotic leak remains a worrisome early postoperative complication following pouch reconstruction. The majority of leaks occur at the pouch-anal anastomosis, but may occur at any suture or staple line. Patients often present with early symptoms of abdominal pain, fever, tachycardia, and potentially hypotension, rendering the diagnosis to be made clinically the majority of the time. However, this is often followed up with imaging, such as cross-sectional imaging or Gastrograffin enema. The morbidity of anastomotic leaks may be monumental, resulting in sepsis, fistulas, strictures, and potentially pouch failure. Therefore, rapid and early diagnosis and treatment of ensuring pelvic sepsis is critical in order to prevent long-term pouch failure.

The overall anastomotic leak rate leading to pelvic sepsis following IPAA has been reported at between 2.9% and 19%. In severe colitis, leak rates have been reported at 5%.

Prevention plays a key role in maintaining the standard of improved quality of life. Techniques aimed at reducing leak rates include ensuring adequate blood supply in preventing ischemia and no tension to the anastomosis. Hence, pouch reconstruction is most often reserved as a subsequent surgery following colectomy in the setting of an acute UC flare or high-dose steroid requirements. Treatment for anastomotic leak varies from medical management to percutaneous drainage to operative intervention. The patient is usually started on antibiotic therapy, bowel rest, and intravenous fluid resuscitation. If nonsurgical methods fail, laparotomy for washout with
drain placement and potential primary repair is possible if tissue integrity and the defect are deemed reparable at the time of inspection. The most drastic repair warrants excision of the pouch if there is clear evidence of irreversible ischemia.

**ABSCESS**

Contrary to common belief, pelvic abscess may form without anastomotic leak. The prevalence of abscess formation reported in various series ranges from 5% to 8%. Diagnosis is achieved via CT imaging and clinical presentation of signs suggestive of sepsis and abdominal pain. In the presence of a sizable pelvic abscess, percutaneous drainage under CT guidance may prevent laparotomy. Antibiotic coverage should also be started, ensuring coverage includes both aerobic Gram-negative and anaerobic organisms. When drain outputs decrease to less than 100 mL over a 24-hour period, a tube or drain contrast study will provide additional information in deciding whether to remove or keep the drain. Late complications from pelvic abscess formation include fistula formation, commonly with the urethra in males and the vagina in females. The etiology of abscess formation in the immediate postoperative period is likely attributed to pouch ischemia or leak, in contrast to late-forming abscesses, which may be suggestive of Crohn’s disease.

**Late Complications**

**POUCH FISTULA**

Pouch fistula is considered a late presenting complication, often following abscess or anastomotic leak, and affects upward of 7% of patients. The median time of presentation following IPAA has been reported as 10 months, but may occur as early as 3 months. The various types of fistula originate from the appendage, pouch-anal anastomosis, inflow limb, and the pouch reservoir proper. The distal connection can vary from the abdominal wall, bladder, small bowel loops, and vagina in women. The pouch-vaginal fistula is the most common form, affecting upward of 16% of women who develop this complication. In order to develop a treatment plan, the origin of the fistula from the pouch must be determined, which can be accomplished by
direct visualization under general anesthesia, poucoscopy, and via Gastrografin enema.

Treatment of pouch-related fistula is complicated by high recurrence rates and imperfect healing, often requiring multiple operations. Repair of pouch-vaginal fistulas is approached depending on the location of fistulization along the vaginal canal. A local approach is perineal or transvaginal. If the fistula arises above the ileoanal anastomosis, the abdominal approach includes primary repair of the vaginal defect, resection of the retained rectum, and mucosectomy with a new ileoanal anastomosis. This option offers the best recovery rates, ranging from 67% to 80%. Perineal or transvaginal approaches involve full thickness flaps and are associated with lower healing success from 35% to 60%. Appendage and bladder-associated fistulas are treated by resection of the appendage and restapling the blind end of the ileum. The bladder fistula is resected and primary closure of the pouch and bladder is performed.

**SMALL BOWEL OBSTRUCTION**

Small bowel obstruction (SBO) is a well-known complication following abdominal surgery, and is no exception after IPAA. The two principle causes of SBO in this setting are due to adhesions and a redundant ileal pouch. With adhesive disease, treatment includes bowel rest, decompression, and resuscitation. Adhesiolysis is indicated when bowel rest fails and clinical symptoms worsen, although care must be taken not to damage the pouch intraoperatively. Non-adhesive obstruction is a later manifestation, presenting months following pouch reconstruction. It occurs as a mechanical obstruction secondary to the pouch having stretched out over time, subsequently flipping onto itself. This warrants surgical repair, at which time the redundant pouch may require resection, since a pexy procedure may only serve as temporary relief.

**STRUCTURE**

Ileal pouch stricture is another late complication occurring in 10% to 40% of cases due to ischemia, pelvic sepsis, or anastomotic leak. The most common locations for stricture formation occur at the pouch- anal anastomosis or proximal to the inflow limb of the pouch. Several series have
evaluated the risk factors for fistula formation, which include pelvic sepsis, handsewn anastomosis, diverting loop ileostomy, mesenteric tension, high body mass index, and NSAID use. Treatment modalities include serial dilations, which demonstrate a high success rate. In the instance that dilations fail, advancement flap anoplasty serves as the surgical treatment of choice.

MANAGEMENT OF POUCH-RELATED COMPLICATIONS

Pouch Dysfunction

Pouch dysfunction is an umbrella term used to define any deviation from normal pouch function, or that which imparts negative impact on the patient’s quality of life. Given the broad application of the term, the literature fails to identify a consistent definition of pouch dysfunction; however, the most common complaints include frequency of bowel movements, incontinence of liquid stool, clustering, urgency, and incomplete evacuation.

Failure of RPC with IPAA occurs from 3.5% to 15%. Salvage surgery exists as a rescue procedure aimed at preserving the existing pouch and anal continence. The majority of patients who undergo salvage surgery often experience severe septic complications that are unamenable to medical therapies. Although surgical repair may successfully save the original pouch, subsequent failure remains an ongoing risk. One Italian series reported higher 5-year failure rates after salvage (28.8%) compared with primary IPAA (5.7%). An overall decrease in bowel frequency and urgency have been reported by patients at 3 years of follow-up.

There is no doubt that a patient experiences a great deal of discomfort and stress related to pouch complications. Although clinicians encounter this scenario not uncommonly, they may not be fully aware of how pouch dysfunction affects the patient. A study by Brandsborg and colleagues revealed that physicians and patients’ perspective on bowel dysfunction differ on parameters such as urgency, frequency, incontinence, and incomplete evacuation. Even expert clinicians overestimated the importance of incontinence and frequency on quality of life and underestimated the impact
of clustering and urgency, compared to how these factors truly mattered to the patient.\textsuperscript{43}

**Pouchitis**

Pouchitis is perhaps the most common long-term complication following IPAA, and significantly impacts the patient’s quality of life and long-term surgical outcome. It represents a spectrum of disease processes with variable risk factors, pathogenic pathways, clinical phenotypes, and prognoses. As a result, an enormous degree of effort and resources have been invested into this complication in hopes of better understanding the root causes of disease and to better prevent it.

There exists a wide range of clinical presentations, manifested by crampy abdominal pain, hematochezia, urgency, and frequency of bowel movements and fevers, all of which are not specific to pouchitis alone. Pouchitis has been reported to occur in up to 40\% of patients within the first year following ileostomy closure.\textsuperscript{56} The natural history of disease mimics that of UC, wherein dysregulated acute flares ultimately result in chronic inflammation. It is generally believed that pouchitis results from alterations in the intestinal microbiome, rendering the genetically predisposed host susceptible to developing abnormal immune responses.\textsuperscript{44}

The risk factors associated with pouchitis have been studied extensively. Several authors have identified factors associated with acute or chronic pouchitis, as scientists are beginning to acquire a better understanding that these presentations are likely two different disease processes.\textsuperscript{57} Smoking has been shown to be associated with acute pouchitis,\textsuperscript{58} whereas long duration of IPAA, extraintestinal manifestation of UC, preoperative thrombocytosis, and postoperative IPAA complications are all associated with chronic pouchitis.\textsuperscript{59}

Pouch endoscopy offers a highly valuable mode of diagnosing pouch disorders. It reveals the severity and extent of mucosal inflammation under direct visualization with the option of obtaining biopsies for histological assessment. Although histology serves a limited role in diagnosing severity of disease, it allows identification of specific features such as metaplasia, viral inclusion bodies (CMV infection), granulomas, and dysplasia.

Treatment is based on the type of pouchitis whether antibiotic-responsive or antibiotic-dependent (those with frequent relapses) to antibiotic refractory
pouchitis. Since the disease is triggered by microbial and immune aberrations, antibiotics serve as mainstream therapy. In antibiotic-responsive cases, first-line therapy includes metronidazole (15-20 mg/kg/d) or ciprofloxacin (1000 mg/d) for 2 weeks’ duration. In the setting of antibiotic-resistant pouchitis, or chronic pouchitis, various immunologic agents, biologics (infliximab), steroids, and anti-inflammatory agents have been used. Management of chronic pouchitis remains a complex and challenging feat, as it is the most common cause of pouch failure. In the instance of resistance to medical therapy, a temporary diverting loop ileostomy may be warranted, versus pouch excision and end ileostomy.

**Cuffitis**

Cuffitis is defined as chronic inflammation or recurrent disease within the remnant rectal mucosa left within the J-pouch. It has been referred to as a variant form of UC in the rectal cuff among patients with IPAA without mucosectomy (Fig. 46-10). As previously discussed, when IPAA is created, a 1- to 2-cm length segment of rectum resulting from the double-stapled technique in J-pouch reconstruction is retained. Few series have reported the incidence of cuffitis to occur in 4% to 17% of patients, and it is a clinically significant risk factor in the development of pouchitis.²⁴,⁶⁰ Clinically, cuffitis is very similar to pouchitis, plagued by pain, low-grade fevers, and bloody stools. Diagnosis is made on endoscopy wherein the rectal cuff appears grossly inflamed in contrast to the remainder of the pouch demonstrating normal appearing mucosa. Mucosal biopsy is often performed providing definitive diagnosis, demonstrating inflammatory cell infiltration and ulceration within the rectal mucosa alone. Treatment is achieved by local therapy such as Canasa suppositories. Persistent or recurrent disease warrants further investigation, as Crohn’s disease cannot be ruled out. Surgical intervention entails mucosectomy of the rectal remnant with pouch advancement.
FIGURE 46-10 Pouch endoscopy revealing cuffitis. The mucosa demonstrates diffuse edema, granularity, and exudate.

Cancer and Dysplasia of the Pouch, Rectal Remnant, and Anal Cuff

Although proctocolectomy eliminates the source of disease, the presumptive concerns over the inherent risk of cancer in the ATZ remain a source of controversy among surgeons. As discussed, the two techniques for RPC and IPAA are the stapled anastomosis versus a handsewn anastomosis. The debate as to whether the remnant rectal cuff poses a significant cancer risk to the patient post-IPAA has led some surgeons to recommend mucosectomy with handsewn IPAA. Numerous studies sought to identify the incidence of ATZ dysplasia or cancer between the stapled IPAA versus mucosectomy with handsewn IPAA, revealing an extremely low overall incidence of dysplasia and adenocarcinoma.\(^{61}\)

Initial studies identified only 19 cases of dysplasia and cancer in the ATZ within the pouch, anal cuff, and ATZ, and interestingly in the majority of
these cases, patients underwent mucosectomy. Recent studies have the benefit of longer follow-up duration, upward of 20 years following IPAA. Silva-Velazco and colleagues assessed a single institution experience on the long-term incidence of ATZ dysplasia among patients who had a stapled IPAA for greater than 20 years, revealing the incidence plateaued at 3.4% without any cases of adenocarcinoma. In the instance of dysplasia and cancer, TPC should include total mesorectal excision. The circumference margin bears a significant prognostic impact on the rates of local recurrence, distant metastasis, and survival; hence, the circumferential margin serves as a surrogate marker of advanced disease as opposed to an indicator of incomplete excision.

Neoplastic changes in the columnar cuff are rare, ranging from 0% to 0.03%. Various studies have identified a close association of dysplasia or cancer after IPAA to be strongly associated with dysplasia or cancer in the resected proctocolectomy specimen. The risk of adenocarcinoma following IPAA in patents with UC is increased with the length of time after surgery, as well the presence of cancer or dysplasia in the original proctocolectomy specimen.

Increasing evidence suggests that long-term and consistent exposure to fecal material in concert with increased microbial burden in the pouch may result in inflammatory changes leading to colonic metaplasia, effectually mimicking UC. To that end, dysplasia and cancer may develop in the remaining rectal mucosa, anal transition zone, or the pouch itself. A systematic review of the literature revealed the cumulative risk of primary pouch-related cancers arising from the anorectal residual mucosa following IPAA is reported at a maximum of 0.4% at 20 years, with several series revealing 0% incidence. It is plausible to venture that IPAA is safe and eliminates an overwhelming cancer risk of colorectal origin.

Surgery is warranted with high-grade dysplasia and cancer diagnoses. Mucosectomy with pouch advancement is generally performed. The approach to a stapled ileoanal anastomosis at the anorectal junction of a stapled IPAA leaves a 1- to 2-cm remnant of rectal mucosa. These patients require continued follow-up for potential neoplastic changes postoperatively. Some authors note that chemotherapy did not negatively influence pouch function, in contrast to radiation therapy, which is associated with poor functional outcomes. Multiple series discovered higher pouch failure rates
among cancer patients compared to non-cancer patients; however, results were not statistically different.\(^\text{28,65}\)

**CONCLUSION**

Patients with UC warranting surgical intervention require a well-established relationship with a gastroenterologist and surgeon. The complexities of this disease are best managed within a team of clinicians who are familiar with and experienced in all aspects of the patient’s ongoing battle with UC. Patients are presented with a multitude of options when considering surgery for UC. It is clear that patients can undergo surgery with reconstruction and maintain an excellent quality of life. They should be fully informed and participatory in all decision-making with clinicians, particularly with respect to the risks, benefits, potential complications, and later implications of each procedure. In addition, the surgeon should be well-versed and experienced in the technical demands of the surgery and pre- and postoperative care in management of complications.

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Ulcerative colitis and Crohn’s disease are gastrointestinal disorders of modern society, and their frequency has increased in developed countries since the mid-20th century. The highest incidence and prevalence of inflammatory bowel disease are seen in North America and Northern Europe, whereas the lowest rates are seen in continental Asia. Despite the use of biologics and other advances in medical treatment, up to 15% to 30% of patients with ulcerative colitis and up to 70% of patients with Crohn’s disease will require surgery during the course of their disease. Recent trends in inflammatory bowel disease have included the increased adoption of a laparoscopic or minimally invasive approach to surgery with the advantages of a faster recovery, fewer complications, less intra-abdominal adhesions, better cosmesis, and a shorter hospital stay. Biologics have changed the medical approach to inflammatory bowel disease, particularly in patients with Crohn’s disease, with an increasing usage of a “top down” approach to treatment in an attempt to rapidly induce remission in patients. With increasing usage of biologics for treatment of inflammatory bowel disease,
there is increasing concern about the risk of infectious complications and other complications in patients on biologics who require surgery and the optimal perioperative management of these agents.

This perspective reviews trends in surgery for ulcerative colitis, the role and results of ileal pouch anal anastomosis surgery, the use of biologics around the time of surgery, and the management of dysplasia and cancer.

ULCERATIVE COLITIS

Since its introduction by Parks and Nicholls in 1978, restorative proctocolectomy with ileal pouch anal anastomosis has become the standard operative approach for the majority of patients who require surgery for ulcerative colitis. Despite over 35 years of experience, the procedure remains technically demanding and is associated with a number of potential complications that are balanced by the patient’s desire to avoid a permanent ileostomy. With appropriate expertise, outcomes are excellent and associated with improved quality of life and high patient satisfaction.

The ileoanal pouch procedure is performed in a staged approach, rarely in a single stage without an ileostomy and most commonly as a 2- or 3-stage procedure (Table 47-1). Indications for surgery for patients with ulcerative colitis include failure of medical therapy, intractable fulminant colitis, toxic colitis, perforation, uncontrolled bleeding, intolerable side effects of medications, strictures, growth retardation in children, high-grade or multifocal dysplasia and dysplasia-associated lesions or masses, and cancer. Patients with acute colitis or fulminant colitis and those who require emergency surgery are generally initially treated with total abdominal colectomy, ileostomy, and Hartmann closure of the rectum. In these nonelective situations, pouch construction is generally felt to be contraindicated.

| TABLE 47-1: RESTORATIVE PROCTOCOLECTOMY: 1-, 2-, AND 3-STAGE PROCEDURES |
Review of the Nationwide Inpatient Sample of over 1.5 million patients with ulcerative colitis admitted to a US hospital from 1991 to 2011 has shown an increase of ulcerative colitis–related admissions of 170% and an increase in the number of patients who required total abdominal colectomy of 44%. In this time period, total abdominal colectomy increased by 15% (compared to proctocolectomy) and, since 2008, was more frequently performed as the initial operation for surgical intervention for ulcerative colitis.

Over the past several decades, there have been a number of refinements in the surgical technique or pouch construction. The ileoanal pouch procedure may be performed as a single stage in carefully selected patients. A number of centers have published series supporting the omission of a diverting ileostomy generally in young, healthy, low body mass index patients who are not anemic, are well nourished, and are not on immunosuppressive medications or biologics. The number of patients who undergo the procedure as a single stage omitting a diverting ileostomy remains quite small. Technical aspects of the surgery in patients who are optimal for omitting a diverting ileostomy include no significant blood loss, no tension on the anastomosis, and a technically excellent procedure. These studies have shown similar results in the diverted and nondiverted groups with respect to leak rates and rates of pelvic sepsis but generally have been biased because the decision for an ileostomy was left to the discretion of the surgeon.
Although the use of an ileostomy does not prevent anastomotic leak, the clinically less severe consequences of the leak and pelvic sepsis in diverted patients is generally felt to have a favorable impact on subsequent pouch success and bowel function.

Pouch configuration, originally described as an S-pouch, now includes the J-pouch, the H-pouch, the S-pouch, and the W-pouch. Due to the ease and speed of construction, the J-pouch is the most common reservoir performed. A meta-analysis compared W-, J-, and S-pouches, and the functional results are essentially equivalent. S-pouches are more likely to require intubation for evacuation, and there was slightly less bowel frequency and need for antidiarrheal medications with W-compared to J-pouches. S-pouches can provide an additional length of several centimeters and may facilitate getting the pouch to reach the anus in cases where a J-pouch will not reach. The efferent limb of the S-pouch, which should be initially constructed to be no longer than 2 cm, may elongate with time and cause obstructed defecation, which may require revision of the limb.

Although mucosectomy and double-stapled procedures are both options for the ileoanal anastomosis, the majority of patients undergo the double-stapled technique, which is technically easier to perform. The potential advantages of the technique include less tension on the anastomosis, ease of technical performance, and potentially improved functional results because of less dilatation of the anal canal and the preservation of the transition zone. In small trials, including 3 prospective randomized trials and 1 comparative study, the functional results of a double-stapled technique and mucosectomy have been similar.

Recent studies have looked at the method of closure of the skin of the ileostomy takedown site and have demonstrated a marked reduction in surgical site infection with a purse string closure compared to primary closure in addition to higher satisfaction with the cosmetic outcome.

A laparoscopic approach is increasingly used for the ileoanal pouch procedure with potential advantages of more rapid recovery and better cosmesis. Most series of laparoscopic pouches are small and avoid patients with a body mass index of greater than 30 kg/m². A Cochrane review of 11 trials and over 600 patients found similar length of stay, morbidity, reoperation, and readmission with a laparoscopic versus open pouch procedures. A laparoscopic approach was associated with longer operating
time, a small incision, and improved cosmesis. An additional advantage of the laparoscopic approach is less intra-abdominal adhesions and less adnexal adhesions, which could result in a decreased risk of infertility and decreased incidence of postoperative bowel obstruction. Laparoscopic approaches include laparoscopically assisted, hand-assisted, and single-incision laparoscopic techniques.

Pouch failure, defined as the need to return to a permanent ileostomy with or without excision of the pouch, occurs in 5% to 10% of patients and may be due to pouch-related complications including pelvic sepsis, anastomotic leak and the development of fistula, the development of previously unsuspected Crohn’s disease, and poor function. Pouchitis, one of the most common complications, occurs in up to 40% of patients within the first 10 years of pouch construction and up to 70% of patients within 20 years of surgery and is a rare cause of pouch failure. The cause of pouchitis remains unknown. The majority of patients respond to antibiotics, whereas a small number of patients have chronic ongoing pouchitis. With increasing years of follow-up, a small cohort of patients may have late pouch failure because of poor bowel function and incontinence as a result of the known decrease in anal sphincter pressures associated with aging and the more liquid frequent bowel movements associated with the pouch.

Since its approval by the US Food and Drug Administration (FDA) for use in the United States for patients with ulcerative colitis in September 2005, increasing numbers of patients with ulcerative colitis have been treated with infliximab, an anti-tumor necrosis factor chimeric antibody. Results on the 3-year efficacy of infliximab as a rescue therapy in a previous placebo-controlled trial of infliximab used in acute steroid-refractory ulcerative colitis showed that after 3 years, 12 (50%) of 24 patients treated with infliximab and 16 (76%) of 21 of patients treated with placebo had required colectomy. The quality of life of the 2 groups was not different, as measured by the Short Form (SF)-36 and the Short Health Score questionnaire at the time of follow-up.

The efficacy of biologic agents needs to be balanced with the morbidity associated with their use, particularly infectious complications. There has been continual debate with respect to the risk of postoperative complications in patients who receive biologics preoperatively. A study from the Mayo Clinic advocated a 3-stage versus a 2-stage proctocolectomy in patients
with ulcerative colitis who were managed preoperatively with infliximab. Thus, initial total abdominal colectomy, ileostomy, and Hartmann closure of the rectum would be performed, which would then allow the patient to come off biologics prior to ileoanal pouch construction. A recent systematic review and meta-analysis looked at 7 papers including 162 patients and 468 controls who underwent primary pouch creation. Studies included in this review have relatively small sample sizes and include heterogeneous study populations. Confounders such as severity of disease and disease duration are not accounted for. In this review, patients who received infliximab were more likely to have early and postileostomy closure ileoanal anastomosis–related complications. Interestingly, use of biologics was associated with a lower surgical site infection rate. Looking at any type of surgery, biologics were associated with a trend toward higher total and higher infectious complications, but the difference was not statistically significant.

With respect to pharmacokinetics, the half-life for elimination of infliximab is between 7 and 18.5 days, and by 12 weeks, the majority of inflammatory bowel disease patients have undetectable levels of infliximab. Should surgery be delayed in such patients for 12 weeks? It is unlikely that this is possible in patients with active ulcerative colitis without resulting in a potential flare of disease.

Patients with ulcerative colitis who are on infliximab presumably have more severe disease and should be considered for a 3-stage procedure with initial total abdominal colectomy and ileostomy followed by pouch creation and then ileostomy takedown. Along with patients who are on high-dose steroids, patients with ulcerative colitis on infliximab should be considered for initial colectomy and not ileoanal pouch creation because of the high risk of complications.

**CROHN’S DISEASE**

Infliximab was first approved by the FDA for use in selected patients with Crohn’s disease in 1998. Despite optimal medical therapy, however, approximately 70% of patients with Crohn’s disease will require surgery within 10 years of diagnosis, and a substantial number of patients will require further surgery for recurrent disease. The use of infliximab and other biologic agents and the development of minimally invasive surgical techniques have
substantially changed the medical and surgical approach to such patients. Although biologics were initially felt to decrease the need for surgery, population-based studies have subsequently failed to demonstrate a reduced need for surgery.

Tumor necrosis factor (TNF)-α plays a role in the immune response, angiogenesis, and collagen synthesis, so a key concern is the risk of the development of infectious complications in patients with Crohn’s disease who are maintained on biologics who require surgery. The results of a number of retrospective studies have been conflicting. A recent systematic review of 2 prior systematic reviews and 6 meta-analyses was performed.16 This review examined all previous reviews, studies, and meta-analyses and included meta-analyses that included only a large number of patients and applied quality assessment. Patients with Crohn’s disease who were treated with anti-TNF agents had an increased risk of postoperative complications including infectious or anastomotic-related complications after abdominal surgery. Although a preoperative drug-free interval may be considered, there may be an appreciable risk of a flare of disease. My approach to intraoperative management is as follows: for patients who are undergoing total abdominal colectomy for colonic Crohn’s and rectal sparing and who are on biologics with or without steroids, I strongly consider fecal diversion with an ileostomy and perform either a Hartmann closure of the rectum or, depending on specific intraoperative factors, a primary anastomosis with a proximal loop ileostomy. For patients who are not candidates for fecal diversion, such as patients with diffuse jejunoileitis who undergo strictureplasty or patients who undergo ileocolic resection (in whom an ileostomy would be in the proximal ileum), increased vigilance in the perioperative period for prompt recognition and treatment of potential septic complications is warranted. In selected patients, a biologic-free period may be considered but is associated with a risk of flare of disease.

**RISK OF CANCER**

Ulcerative colitis and Crohn’s disease are both associated with an increased risk of colorectal cancer compared to the general population. A population-based series has reported an annual incidence rate of 0.06% to 0.2%, and a meta-analysis showed rates of 2.1%, 8.5%, and 17.8% at 10, 20, and 30
years, respectively. Risk factors for the development of colorectal cancer in patients with ulcerative colitis include pancolitis, prolonged disease duration (>8 years), diagnosis at a young age, family history of inflammatory bowel disease, and associated primary sclerosing cholangitis. In patients with Crohn’s disease, the risk factors are similar, although the association of cancer in patients with primary sclerosing cholangitis and Crohn’s does not appear to be as strong. In addition, inflammatory pseudopolyps are also thought to increase the risk of cancer probably from longstanding inflammation, which is believed to be a risk factor for progression to colorectal cancer. Although surveillance colonoscopy is recommended, there is no clear evidence (based on a Cochrane review) that survival is improved in patients with extensive colitis. However, cancers that were detected appeared to be detected at an earlier stage. Colonoscopic surveillance includes 2 sets of 4-quadrant biopsies in each segment of the colon (right, transverse, left, and rectum), which yield approximately 32 biopsies. Other groups have shown that 33 biopsies per examination were necessary to exclude a diagnosis of dysplasia with 90% confidence. A major limitation of optical colonoscopy is the difficulty in detecting dysplasia by visualization of the mucosa by the endoscopist. To potentially enhance the detection of dysplasia, targeted biopsies with use of magnification chromoendoscopy can be used. With this technique, indigo carmine or methylene blue is used and sprayed over the mucosa of the colon and rectum to improve the visualization of the mucosa. The uptake of the methylene blue dye is different for dysplastic compared to colitic mucosa; the use of indigo carmine details the space between the colonic crypts (facilitating detection of dysplastic tissue from colitis tissue). This technique may be combined with either narrow-band imaging or confocal laser endomicroscopy to further enhance the detection of dysplasia. An advantage of these techniques includes increased detection of dysplastic lesions. Despite this, at present, there are no longitudinal studies showing that the increased detection of lesions resulting from chromoendoscopy decreases cancer-related morbidity or mortality. Switching to chromoendoscopy may increase yield on dysplasia and increase number of colectomies without impacting on mortality and morbidity. The role of chromoendoscopy has promise and continues to evolve.

Patients with pancolitis who have had symptoms for 8 or more years should undergo surveillance colonoscopy every 1 to 2 years. Total proctocolectomy with or without ileal pouch–anal anastomosis is the
recommendation for patients with cancer, non–adenoma-like dysplasia-associated lesion or mass, or high-grade dysplasia.\textsuperscript{21} The management of low-grade dysplasia in the setting of ulcerative colitis remains somewhat controversial. Progression to high-grade dysplasia rates vary widely from 0\% to over 50\%. There may be a role for chemoprevention with 5-aminosalicylic acid (5-ASA), but there are little prospective data. One meta-analysis of 9 observational studies showed a reduced risk of developing colorectal cancer or dysplasia with 5-ASA use.\textsuperscript{22}

Following restorative proctocolectomy, routine surveillance of the ileal pouch mucosa for detection of dysplasia is generally not recommended.\textsuperscript{21} A small number of pouch-related cancers have been reported, mainly in patients who had colorectal cancer and/or dysplasia at the time of initial pouch construction. Similarly, there is also little evidence to support routine surveillance of the 1- to 2-cm rectal cuff; however, there may be residual inflammation in this area, and a small number of cancers have been reported. Selected surveillance may be performed and patients counseled as to the potential risk of cancer. Patients with small bowel Crohn’s disease are also at increased risk for small bowel cancer. When performing a strictureplasty, biopsy of the mucosa has been suggested.

REFERENCES


OVERVIEW

Hereditary colon cancer is a heterogeneous conglomeration of genetic defects that are mostly autosomal dominant in nature and lead to variable risk of colon cancer and other associated cancers. Some of these syndromes are characterized by the formation of traditional adenomas and are caused by defects in tumor suppressor genes and others are in mismatch repair genes. The most common of these include mutations in the tumor suppressor adenomatous polyposis coli (APC) gene that is associated with familial polyposis. Genetic defects in tumor mismatch repair genes (MLH1, MSH2, MSH6, PMS2, and EPCAM) are also associated with the development of adenomas, and these occur in multiple genes that are associated with tumors that have high levels of microsatellite instability (MSI). Finally, there is a
group of less common genetic defects that result in hamartomatous polyposis syndromes such as juvenile polyposis and Peutz-Jeghers syndrome, to name the two most common. We will outline the genetic defects, epidemiology, diagnosis, clinical manifestations, and clinical management for these syndromes.

FAMILIAL ADENOMATOUS POLYPOSIS

Introduction

Familial adenomatous polyposis (FAP) is an inherited condition characterized by thousands of polyps in the colon. FAP occurs with a frequency of about 1:10,000 to 1:18,000 live births in Northern Europe and other similar Caucasian populations.\(^1\)\(^-\)\(^3\) It accounts for less than 1% of all colorectal cancers. Males and females are affected equally.

Genetics

FAP is an autosomal dominant colorectal cancer syndrome caused by a germline mutation in the APC gene, located on chromosome 5q21-22. The APC gene is a tumor suppressor gene that functions by suppressing the formation of adenomas in the colon and tumors elsewhere in the body. Approximately 10% to 25% of germline APC mutations are new in individuals without a family history of FAP.\(^3\)\(^-\)\(^5\) There is nearly 100% penetrance of the colonic manifestations of FAP but variable penetrance of the extracolonic manifestations of the disease.\(^6\)

Patients with FAP who inherit a single APC mutation acquire a somatic mutation (or “second hit”) in the second allele of the APC gene. A cell with this functional loss of the APC gene has no functional APC protein. This leads to defects in the Wnt signaling pathway, abnormal intracellular accumulation of beta-catenin, unregulated cell growth and division, and formation of adenomas.\(^7\)\(^,\)\(^8\) Over 1000 different mutations in the APC gene associated with FAP have been described, and the location of the mutation may influence the phenotypic expression. In other words, there is variable phenotypic expression depending on the location of the mutation in the gene.\(^9\)
For example, patients with mutations near codon 1300 generally develop particularly severe disease with over 1000 polyps and earlier cancer onset.\(^9,^{10}\) Attenuated FAP (<100 colorectal adenomas) is associated with mutations before codon 157 and after codon 1595.\(^{10}\) Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is associated with mutations between codons 311 and 1444. Mutations after codon 1444 have been linked to the development of desmoid tumors.\(^{10,11}\)

**Clinical Manifestations**

In addition to the numerous colorectal adenomas that characterize FAP, there are a variety of extracolonic manifestations with variable phenotypic expression. Initially, most patients with FAP are asymptomatic. Patients who develop cancer may present with rectal bleeding, abdominal pain, and loose stools. Patients with desmoids can have abdominal pain or bowel obstruction. Finally, patients can develop symptoms from duodenal adenomas and various skin lesions as well.

**COLONIC**

Classic FAP is characterized by >100 colorectal adenomatous polyps prior to age 40. Nearly 100% of people with FAP will develop colorectal cancer because of the sheer number of adenomas that develop at an early age. One or more of these polyps usually progresses to form a cancer. Polyps usually start appearing in the late teens to early twenties, and progress to cancer by age 40.

Attenuated FAP is characterized by at least 10 to 20 adenomas, but fewer than 100. Patients usually present later in life than those with classic FAP, and have later onset of colorectal cancer (mean age 55).\(^{12}\) In attenuated FAP the polyps are found more frequently proximal to the splenic flexure.

**EXTRACOLONIC**

Extracolonic manifestations of FAP include upper gastrointestinal polyps that occur in nearly all patients with FAP. Fundic gland polyps occur in most patients with FAP; they are small and rarely progress to cancer.\(^{13,14}\) In contrast, gastric adenomas are much less common in patients with FAP, are typically located in the antrum, and have a relatively low risk of cancer.
progression. Around 90% of patients with FAP will develop duodenal adenomas; however, only about 5% progress to duodenal cancer. Approximately half of duodenal cancers are ampullary or periampullary.

**DESMOID TUMORS**

After colorectal cancer and duodenal cancer, desmoid disease is the third leading cause of death in FAP patients. Desmoid tumors are usually found in an intra-abdominal location, especially in the small bowel mesentery and in the abdominal wall. Risk factors for development include trauma, prior surgery, and female sex. In fact, delay of prophylactic colectomy is advocated in patients at high risk for intra-abdominal desmoid disease, if safe. Surgery is to be avoided if possible for intra-abdominal desmoids as the majority are in the small bowel mesentery and can lead to extensive loss of bowel and bleeding. The primary treatment is medical, and includes NSAIDs and antiestrogen therapy. More aggressive regimens include vinblastine/methotrexate and doxorubicin/dacarbazine, and imatinib.

**OTHER EXTRA-INTESTINAL MALIGNANCIES**

These include thyroid cancer, which is usually papillary, and presents in the second or third decade of life. Lifetime risk is about 2%. Annual physical exam with or without neck ultrasound is generally recommended. Other associated tumors such as pancreatic adenocarcinoma, hepatoblastoma, medulloblastoma, and adrenal and biliary cancers have risks <2% in FAP patients, and therefore surveillance tests are not generally recommended unless there is a strong family history.

CHRPEs are characterized by hyper- or hypopigmentation of the retinal epithelium that have no effect on vision. They are present in over 75% of FAP patients and can act as a screening tool or marker for FAP. Gardner syndrome was a term used to describe the constellation of colonic polyposis with a number of extracolonic manifestations including sebaceous or epidermoid cysts, lipomas, osteomas, fibromas, supernumerary teeth, gastric fundic gland polyps, desmoid tumors, juvenile nasopharyngeal angiofibromas, and CHRPE. Now that it is clear that mutations in the
APC gene are the underlying cause of both Gardner syndrome and FAP, the term “Gardner syndrome” is obsolete as it is not a distinct entity.\textsuperscript{6}

**Diagnosis**

FAP should be suspected in any patient who is found on colonoscopy to have ten or greater colorectal adenomas. The diagnosis of attenuated FAP (AFAP) should be suspected in any patient who has ten or greater colorectal adenomas over a lifetime. In addition, FAP should be suspected if a patient has a history of colorectal adenomas plus extra-intestinal features of FAP such as duodenal/ampullary adenomas, papillary thyroid cancer, CHRPE, desmoid tumors, epidermal cysts, or osteomas.

The National Comprehensive Cancer Network (NCCN) recommends APC gene testing for persons with a personal history of 20 or greater adenomas, or a known deleterious APC mutation in the family. Per the NCCN guidelines (version 2; 2016) APC and MUTYH gene testing should be considered for patients with a personal history of desmoid tumor, hepatoblastoma, cribiform morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE. Patients who also have between 10 to 20 adenomas should also be tested for APC and MUTYH mutations.

If a mutation is found, mutation-specific genetic testing should be offered to at-risk family members. This includes all first-degree relatives of the index case and all first-degree relatives of those found to have the APC mutation. The age of testing generally begins around age 10 to 12 years, but may be earlier if the age of onset of polyps in the family is younger. If the familial mutation is found and an individual does not have it, that person can be discharged from surveillance, as they do not have FAP.\textsuperscript{22} If a mutation is not found in an affected patient, then the patient and at-risk family members must be under regular surveillance. Genetic counseling should be offered prior to any genetic testing.

**Screening**

NCCN Guidelines (version 2; 2016) recommends that patients with a positive APC mutation should have a colonoscopy every 12 months beginning at age 10 to 15 years. Patients should continue to undergo colonoscopic surveillance
while awaiting colectomy. Esophagastroduodenoscopy (EGD) screening and thyroid ultrasound screening begin around age 20.

In patients with a known familial positive APC gene for attenuated FAP, colonoscopy begins in the late teens and continues every 2 to 3 years, unless polyps are identified. Upper endoscopy should start at age 20 to 25 years as well as an annual thyroid exam. If genetic testing is uninformative or a patient has not been gene tested, screening should still be performed.

**Management and Surveillance**

In a patient with FAP, colorectal cancer is usually inevitable, so the goal is prevention with either colectomy or proctocolectomy. The timing of surgery and type of operation is individualized based on the patient’s polyp burden, family history of age of cancer/polyp formation, and risk of desmoid formation. Most patients with classical FAP undergo surgery between the ages of 16 and 20 years.

Total abdominal colectomy (TAC) with ileorectal anastomosis can be considered if the rectal polyps are amenable to endoscopic surveillance and resection. It is technically simpler than a proctectomy, has a good functional outcome, avoids a permanent stoma, and avoids the risk of sexual or bladder dysfunction and decreased fecundity that can occur following proctectomy. The disadvantage, however, is risk of cancer in the remaining rectum. The rectum must be closely surveyed at least annually.

Total proctocolectomy (TPC) with or without ileoanal pouch (ileal pouch-anal anastomosis [IPAA]) is recommended for patients with profuse polyposis or rectal cancer. While TPC with end ileostomy eliminates the risk of colorectal cancer, TPC with IPAA leaves a risk of cancer in the pouch and anal transition zone, and thus requires surveillance. The disadvantages of a rectal dissection include risk of sexual or bladder dysfunction, need for temporary or permanent ileostomy, and variable function (with IPAA).

If the polyps are controlled endoscopically in patients with attenuated FAP, then they may not need a colectomy. If cancer occurs or the polyp burden becomes too great, TAC with ileorectal anastomosis is usually sufficient, as the polyps are most often right-sided. Of course, if polyps are found more distally, then TPC must be entertained.

Surveillance following colectomy or TPC includes endoscopic evaluation
of the rectum or ileal pouch every year and of the ileostomy, if present, every 2 years. Chemoprevention has been entertained to manage the rectum postop. There are currently no FDA-approved medications for this indication. While there are data to suggest that Sulindac is the most potent polyp regression medication, it is not known if the decrease in polyp burden decreases cancer risk.

**UPPER GI POLYPOSIS**

In patients with classic or attenuated FAP, the American College of Gastroenterology recommends screening for gastric and proximal small bowel tumors using an upper endoscopy including duodenoscopy starting at age 25 to 30 years. The Spigelman staging system of duodenal polyps (based on polyp number, size, histology, and degree of dysplasia) allows for an objective assessment of duodenal polyposis and thus recommended surveillance intervals. Surveillance should be repeated every 0.5 to 4 years depending on the Spigelman stage of duodenal polyposis: 0 = 4 years, I = 2 to 3 years, II = 1 to 3 years, III = 6 to 12 months, IV = surgical evaluation. Examination of the stomach should include random sampling of fundic gland polyps. Low-grade dysplasia is common in fundic gland polyps, and surgery should be reserved for high-grade dysplasia or cancer.

Treatment for duodenal polyposis includes endoscopic and surgical options; pharmacologic agents, namely, NSAIDs, have been used for early disease, although benefits have not been proven. Endoscopic resection with polypectomy or endoscopic mucosal resection for more advanced polyps, and endoscopic thermal ablation of duodenal polyps are all options, although these may have high rates of recurrence. According to the NCCN guidelines (version 2; 2016), surgery is recommended for invasive carcinoma as well as for dense polyposis or high-grade dysplasia that cannot be managed endoscopically. Premalignant lesions may be locally excised via duodenotomy if possible, otherwise pancreas-sparing duodenectomy or pancreaticoduodenectomy is needed, as they are for invasive cancer.

**THYROID CANCER**

Annual thyroid screening by ultrasound is recommended for patients with FAP and attenuated FAP starting in the late teens.
Summary FAP

Familial polyposis is due to genetic defects in the adenomatous polyposis coli tumor suppressor gene. Depending on the location of the mutation in the gene, there is variable phenotypic expression of the disease. Patients with fullblown FAP generally present in their teens and twenties with hundreds to thousands of polyps, and virtually 100% of these patients end up with colorectal cancer if left untreated by the age of 40. These patients are best managed with TPC with either ileorectal J pouch or an ileostomy. Patients with attenuated FAP present in their 40s to 60s with tens to a hundred polyps. These patients often have rectal sparing from the polyps and an intermediate operation of TAC with ileorectal anastomosis and surveillance of the retained rectum. Thyroid cancer, desmoids and duodenal and gastric lesions also require close attention.

MUTYH POLYPOSIS

Introduction

MUTYH-associated polyposis (MAP) is an autosomal recessive condition associated with an increased risk of colorectal cancer and the early development of multiple adenomatous polyps. This is often referred to as the recessive form of familial polyposis, as many of the clinical manifestations are very similar. Patients with biallelic MYH mutations account for less than 1% of all colorectal cancer cases. Some patients will develop fewer than 100 polyps, while others may have hundreds.

Genetics

MAP is an autosomal recessive polyposis caused by biallelic (homozygous or compound heterozygous) mutations in the MUTYH gene. MUTYH is a base excision repair gene, and thus is involved with correcting the effects of oxidative damage to the DNA. This leads to a G:C → A:T transversion in the APC and KRAS genes and hence adenomatous polyposis and serrated polyps. The two most prevalent MUTYH mutations in individuals of
European descent with MAP are two missense mutations, Y179C and G396D. Although many other distinct MUTYH mutations have been found, approximately 90% of Western MAP patients have at least one of these two mutations.\textsuperscript{17,33}

**Clinical Manifestations**

Colonic and extracolonic manifestations can be present in patients with MUTYH-associated polyposis. The colonic phenotype in patients with MAP can be variable, but patients with MAP usually develop 10 to 100 colorectal polyps.\textsuperscript{17,32} Colorectal cancer develops at an average age of 48 years. Although patients with MAP predominantly have adenomas, multiple hyperplastic and/or sessile serrated polyps may occur. Patients with MAP have an approximate lifetime risk of colorectal cancer (CRC) of 70% to 75% while those with a monoallelic MUTYH mutations may only have a marginally increased risk.\textsuperscript{17,34,35}

Data on extracolonic manifestations of MAP are limited. However, there does appear to be an increased risk of duodenal cancer.\textsuperscript{36} Other extracolonic findings include gastric polyps, endometrial cancer, breast cancer, ovarian cancer, bladder cancer, various skin cancers, thyroid cancer, sebaceous gland adenomas, lipomas, CHRPE, osteomas, desmoid tumors, and epidermoid cysts.\textsuperscript{17,36}

**Diagnosis**

Patients with at least 10 adenomas in their lifetime, a known family germline mutation, or a history of adenomas in combination with extracolonic features associated with MUTYH-associated polyposis (duodenal adenomas, desmoid tumors, thyroid cancer, CHRPE, epidermal cysts, or osteomas) should be considered for genetic testing for MUTYH-associated polyposis.\textsuperscript{17,37} The family history follows an autosomal recessive pattern of inheritance. The diagnosis is established by biallelic germline mutations in the MUTYH gene. If the mutation is found, mutation-specific genetic testing should be offered to at-risk relatives of the index case.
Management and Surveillance

Patients at risk for or affected with MAP should undergo yearly colonoscopy starting at puberty. If the polyp burden becomes unmanageable, or if cancer is present, then colectomy is indicated. The type of operation depends on rectal polyp burden. As for AFAP, if the rectum is manageable endoscopically, then total colectomy with ileorectal anastomosis can be entertained. TPC (with or without restoration) may be needed if the rectal polyp burden is unmanageable. Surveillance following colectomy or TPC includes endoscopic evaluation of the rectum or ileal pouch every year, and of the ileostomy, if present, every 2 years.

Just as in patients with classic or attenuated FAP, the American College of Gastroenterology recommends MAP patients undergo screening for gastric and proximal small bowel tumors using an upper endoscopy including duodenoscopy starting at age 25 to 30 years.

There is no consensus as to whether monoallelic MUTYH mutations warrant increased CRC screening.

Summary MUTYH Polyposis

MUTYH polyposis is a defect in an autosomal recessive base excision repair gene. It is often called the recessive familial polyposis. Surgical therapy for the colon is predicated upon the number and distribution of polyps in the colon. It is generally best treated with TPC with ileoanal J pouch for patients with rectal involvement and TAC with ileorectal anastomosis for patients with a spared rectum. Although it is a different genetic defect, the management principles are like those for FAP. The surgeon should also be mindful that carriers of the recessive gene are at increased risk of colorectal cancer as well.

HEREDITARY NONPOLYPOYSIS COLORECTAL CANCER

Introduction
Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is the most common form of inherited colon and rectal cancer. It is responsible for approximately 3% of all cases of both endometrial and colon cancer. It is inherited in an autosomal dominant fashion. Affected kindreds are characterized by multigenerational involvement, with the offspring of affected individuals having a 50% chance of inheriting the disorder such that in large kindreds several offspring can be affected. Individuals often have more than one index cancer and generally the cancers present before the age of 50 years. The most common cancers with associated lifetime risks without surveillance are colorectal cancer (80%), uterine cancer (50%), ovarian cancer (20%), transitional cell carcinoma (5%), gastric cancer (5%), and cancers of the pancreas (1%), small intestine (1%), and the biliary system (1%). Some families are also affected with prostate and breast cancer. The genetic defects responsible for HNPCC are germ line mutations in a DNA mismatch repair (MMR) gene. For the most part, tumors in affected patients have loss of MMR as well as being high in MSI. The diagnosis of HNPCC requires a high index of suspicion combined with sound interpretation of MSI status and immune-histochemical (IHC) staining in patients at risk. In patients with a suggestive clinical and family history if MSI status and IHC staining indicate HNPCC, germline testing should be undertaken.

**Genetics**

The most common MMR mutations identified are MLH1 (chromosome 3p21) in 37% of affected individuals, MSH2 (chromosome 2p16) in 41% of affected individuals, MSH6 (chromosome 2p16) in 13% of affected individuals, and PMS2 (chromosome 7p22) in 9% of affected individuals. In an even smaller group of patients a genetic defect in the 3′ end of the epithelial cell adhesion molecule (EPCAM) carries over to the neighboring MSH2 gene, silencing the MSH2 gene, resulting in HNPCC. These patients are at increased risk of colon cancer but generally not the extracolonic cancers such as uterine cancer. Defects in the EPCAM gene on chromosome 2 account for less than 3% of cases of HNPCC. Dr. Henry T. Lynch of Creighton University first identified two kindreds in 1966 with the clinical features of HNPCC. The actual responsible genes were finally identified in the 1990s independently and simultaneously by the laboratories of Dr. Richard Kolodner at Dana Farber Cancer Institute and Dr. Bert Vogelstein at
Defects in MMR proteins result in an increased risk for the development of a multitude of cancers. These genes are responsible for repairing erroneously substituted base pairs, and insertions and/or deletions of segments of DNA that occur during cellular replication and division. Affected individuals have a mutation at one allele, and the second allele is usually inactivated by a variety of mechanisms that then results in failure to repair the aforementioned DNA mismatches. The regions most often affected are areas of repetitive nucleotide sequences called microsatellites. Hence a common feature of HNPCC is high levels of MSI. In turn, MSI affects genes that regulate cell death and growth, resulting in unregulated cell growth and/or cell death and thereby cancer.\textsuperscript{41} In the last 25 years since the discovery of the MMR genes responsible for HNPCC identification, management and surveillance of affected individuals and their families has dramatically improved. The risk of developing cancer in known MMR carriers by each gene is lower than in the past. Table 48-1 identifies the risk of each cancer depending on which gene is affected. Genetic defects in the PMS gene are rare and hence fewer patients with these mutations were identified and followed prospectively. Generally, it is felt that the risk for each of these cancers is even less in patients with a PMS 2 mutation.\textsuperscript{42}

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>46%</td>
<td>43%</td>
<td>15%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>43%</td>
<td>57%</td>
<td>46%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>10%</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Upper GI cancers</td>
<td>21%</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>(bile duct, pancreas, duodenum, and gastric)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract cancers</td>
<td>8%</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>17%</td>
<td>32%</td>
<td>18%</td>
</tr>
<tr>
<td>Brain cancer (glioblastoma)</td>
<td>1%</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Clinical Manifestations

As previously mentioned, HNPCC is characterized by a multigenerational pattern with multiple affected family members with multiple cancers at a younger age than when diagnosed in a sporadic fashion. The average age at diagnosis for a patient with sporadic colon cancer is 70, whereas in HNPCC it is between 45 and 60 years of age. Moreover, up to 7% of patients with HNPCC have a synchronous cancer or multiple cancers at the time of diagnosis. In patients with documented HNPCC, the recommended operation is a TAC with ileorectal anastomosis or a subtotal colectomy with an ileosigmoid anastomosis. In patients who have only a segmental colectomy or an isolated rectal resection, the risk of metachronous cancers is shown in Table 48-2.

| TABLE 48-2: APPROXIMATE RISK OF METACHRONOUS CANCER IN HNPCC WHEN FIRST CANCER IS TREATED WITH A SEGMENTAL RESECTION |
|-----------------|-----------------|-----------------|
| Colon Cancer    | Rectal Cancer   |
| 10 years        | 15%             | 20%             |
| 20 years        | 40%             | 45%             |
| 30 years        | 60%             | 70%             |

The increased risk for metachronous cancers outlined above underscores the importance of a high index of suspicion for HNPCC in patients diagnosed with either colon cancer at a young age and/or multiple cancers and/or those with multiple affected relatives with cancers of the gastrointestinal, genitourinary, and gynecologic organ systems. The name for Lynch syndrome (HNPCC) can be misleading and cause some people to assume that these cancers develop in the absence of polyps. HNPCC is so named to distinguish Lynch syndrome from traditional FAP, which has hundreds to thousands of polyps. HNPCC develops usually from a single polyp that tends more often to be flatter, villous, and located in the right colon than that seen in individuals with sporadic colon cancers. Moreover, the characteristic histopathologic features associated with HNPCC are such that these tumors have a higher incidence of mucinous and signet cell histology, tend to be
poorly differentiated, and tend to have a lymphocytic Crohn’s-like infiltrate.\textsuperscript{49,50} The progression from an adenoma to an invasive cancer is also more rapid in patients with HNPCC, being on the order of 1 to 2 years versus 10 years.\textsuperscript{51-53}

The most common extracolonic manifestations of HNPCC are cancers of the gynecologic (uterine and ovarian cancer) and genitourinary system (see \textit{Table 48-1}). Although colon cancer and endometrial cancer are the most commonly recognized cancer in HNPCC, careful attention must be paid to all associated cancers. The penetrance in patients who have a MMR defect is not 100%, and careful screening and surveillance reduces the risk of both subsequent cancers and death.

\section*{Diagnosis and Management}

Considerable effort has been placed on early diagnosis based on clinical criteria. This helps identify at-risk individuals for treatment, screening, and surveillance. The most accepted clinical criteria are the Amsterdam I (\textit{Table 48-3}), defined in 1990 and Amsterdam II (\textit{Table 48-4}), defined in 1999.\textsuperscript{54,55} Additional clinical criteria include the Bethesda (\textit{Table 48-5}), defined in 1997\textsuperscript{56} and the revised Bethesda (\textit{Table 48-6}), defined in 2004.\textsuperscript{57} The Amsterdam criteria are the most commonly utilized. The 3-2-1 rule of thumb makes it easy to remember these criteria. Amsterdam I criteria applied only to patients with colorectal cancer. There had to be three affected family members where one was a first-degree relative of the other two affected individuals. Two generations had to be involved and one person had to be diagnosed prior to the age of 50 years. Amsterdam II criteria were expanded to include patients with extracolonic index cancers. In both sets of the Amsterdam criteria, familial polyposis had to be excluded as a cause for the cancer. The Bethesda criteria were created to determine which colorectal tumors and extracolonic tumors should have MSI testing. In addition, several prediction models have been developed to aid in assessing which patients with appropriate clinical criteria will have a positive MMR genetic test. In fact, these prediction models are often used to determine that patients with a less than 5% chance of having a positive test should not have germline testing, as it is not cost effective. The most prominent models are the MMRpredict model,\textsuperscript{58,59} the MMRpro model,\textsuperscript{60} and the PREMM model.\textsuperscript{61}
TABLE 48-3: AMSTERDAM I CRITERIA (1990)

1. Three relatives with colorectal cancer with one whom is a first-degree relative of the other two.
2. These three relatives must involve two successive generations.
3. One person must be diagnosed before the age of 50 years.
4. Familial polyposis coli must be excluded.

TABLE 48-4: AMSTERDAM II CRITERIA (1999)

1. Three or more relatives with a HNPCC-associated cancer (colon, uterus, urinary tract, ovary, small intestine, stomach, hepatopancreatobiliary).
2. Two or more successive generations.
3. One person must be diagnosed before the age of 50 years.
4. One person must be a first-degree relative of the two affected individuals.
5. Familial polyposis coli must be excluded.
6. Histologic confirmation of the index cancer.

TABLE 48-5: BETHESDA CRITERIA (1997)

1. Individuals with cancer in families that meet the Amsterdam criteria
2. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional cell carcinoma of the renal pelvis or ureter)
3. Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age <50 yrs, and the adenoma diagnosed at age <40 yrs
4. Individuals with colorectal cancer or endometrial cancer diagnosed at age <50 yrs
5. Individuals with right-sided colorectal cancer with an undifferentiated
pattern (solid/cribriform) on histopathology diagnosed at age <50 yrs
6. Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <50 yrs
7. Individuals with adenomas diagnosed at age <40 yrs

**TABLE 48-6: REVISED BETHESDA CRITERIA (2004)**

1. Colorectal cancer diagnosed in a patient who is less than 50 yrs of age
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors (colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, small bowel, brain, and sebaceous gland adenomas and keratoacanthomas), regardless of age
3. Colorectal cancer with the MSI-high histology (presence of tumor infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient who is less than 60 yrs of age
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 yrs
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

In addition to the outlined clinical criteria and above prediction models, some advocate for direct tumor testing for MMR defects, MSI testing, and/or IHC for MMR on tumor tissue. Many strategies exist using combinations of these tests. No method is 100% sensitive or specific for making the diagnosis of HNPCC. Ultimately the diagnosis is made by a combination of clinical suspicion, MSI and IHC testing on the tumor, and then confirmatory germline testing on known true positives in a kindred suggestive of HNPCC.

In several instances, conflicting data exists such that it appears a patient has HNPCC when in reality the cancer is sporadic. Some examples of this include hypermethylation of MLH1 promoter, loss of heterozygosity of the normal allele, and double somatic mutations in an MMR gene. In some instances of IHC staining, tumors will have a loss of IHC staining in MLH1 and PMS2. This is due to the hypermethylation of the MLH1 promoter (a
somatic defect) and this leads to loss of the function of MLH1 and a MSI-H tumor. At this point, testing for BRAF mutations is essential to rule out Lynch syndrome. A wild-type BRAF gene is unusual in a Lynch cancer. So an MSI-H tumor with a BRAF mutation is almost always due to a somatic mutation that leads to promoter hypermethylation and loss of MLH1 function and not a true Lynch syndrome cancer.\textsuperscript{62-64} The management of patients with HNPCC requires a multidisciplinary approach. The first step is the identification and testing of at-risk patients and their families, followed by treatment of known cancers and then screening and surveillance of patients with a known MMR genetic defect.

**Screening**

**COLORECTAL CANCER**

Patients with known Lynch syndrome should have a yearly colonoscopy.\textsuperscript{52,65} Those with a known MMR defect should start screening at the age of 25 or 5 years prior to the age of earliest diagnosis of a cancer in their family, whichever age is earlier.\textsuperscript{17,66} Early and diligent colonoscopy has been shown to reduce the risk of colorectal cancer as well as the mortality in affected individuals.\textsuperscript{67}

**GYNECOLOGIC MALIGNANCY**

Women with known Lynch syndrome should have a yearly exam with their gynecologist to include an endometrial biopsy and a transvaginal pelvic ultrasound to evaluate the ovaries. Checking the CA-125 tumor marker is advocated by some clinicians every 6 to 12 months. Screening for gynecologic malignancy should start in the beginning of the fourth decade (30 years of age). Moreover, prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy is recommended once childbearing is completed or at any time a colectomy is needed if it has not already been done.\textsuperscript{68}

**GASTRIC CANCER**

There is little evidence that prophylactic screening for gastric cancer in
Lynch syndrome patients reduces the risk of gastric cancer. Despite the lack of efficacy, most groups recommend every-3-year EGD with *Helicobacter pylori* testing at the same time as the colonoscopy. For patients with a history of gastric cancer in the kindred, yearly EGD is recommended. Due to the lethality of gastric cancer, most clinicians tend err on the side of caution and recommend screening, especially since this procedure can be done concomitantly with the yearly colonoscopy.

**SMALL INTESTINE CANCER**

There is no role for routine screening of the small intestine in patients with Lynch syndrome. For patients with a family history of small intestine cancer and/or iron deficiency anemia or unexplained gastrointestinal (GI) symptoms, a wireless capsule endoscopy or magnetic resonance (MR) enterography can be performed every few years. 69

**PANCREATIC CANCER**

Once again, the lifetime risk of pancreatic in known carriers of an MMR defect is approximately 1%, so screening is not recommended for everyone. Lynch syndrome patients with a single first-degree relative with a history of pancreatic cancer should be considered for screening with yearly magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) of the pancreas. If a kindred has multiple instances of pancreatic cancer in non–first-degree relatives, careful consideration for screening should be undertaken. 17,70

**URINARY TRACT CANCER**

Urine cytology and urinalysis can be performed starting at the age of 30. However, in families without a known history of genitourinary tract tumors, sensitivity and specificity are low for the detection of urinary tract cancers. Certainly MMR defect carriers with gross or microscopic hematuria require further investigation of the genitourinary tract with ultrasound and/or CT imaging as well as cystoscopy. It is reasonable to screen Lynch families with a known history of urothelial cell carcinoma with yearly urine cytology and urinalysis. 17
SKIN CANCER

Yearly dermatologic exam to identify sebaceous adenomas and sebaceous adenocarcinoma should be undertaken. In a patient who has a sebaceous neoplasm, a directed family history focusing on Lynch syndrome–associated cancers should be performed.

PROSTATE, BREAST, AND CENTRAL NERVOUS SYSTEM

Yearly screening for prostate and breast cancer as directed for the general population should suffice for patients with Lynch syndrome. Any central nervous system (CNS) symptoms should be promptly investigated.

Surgical Management of Colorectal Cancer

The preferred treatment of colon cancer and endoscopically unresectable adenomas in patients with HNPCC is TAC with ileorectal anastomosis or subtotal colectomy (STC) with ileosigmoid anastomosis. A segmental colectomy leaves behind at-risk colon and makes screening more difficult because a full colonoscopy with a complete bowel preparation is required. The TAC or STC operations provide risk reduction by removing additional at-risk colon and make future screening much easier, as only a flexible sigmoidoscopy is needed. Moreover, most patients have excellent function, with an average of 3 to 4 bowel movements (BMs) daily with either a TAC or STC. Patients who have a segmental colectomy are at increased risk for metachronous colorectal cancer (see Table 48-2) as well as adenomas. Patients with Lynch syndrome and rectal cancer pose a unique problem. Sphincter preservation is usually desired but risks a second surgery as these patients are at increased risk for metachronous colon cancers (see Table 48-2). Moreover, a more complex reoperation in the pelvis is a real risk. Hence there are four main operations outlined below for this cohort of patients. Each operation has its risks and benefits (Table 48-7):

<p>| TABLE 48-7: RISKS AND BENEFITS OF OPERATIONS FOR RECTAL CANCER IN LYNCH SYNDROME |</p>
<table>
<thead>
<tr>
<th></th>
<th><strong>Risks/Negative Aspects</strong></th>
<th><strong>Benefits/Positive Aspects</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>LAR</td>
<td>At-risk colon</td>
<td>Intact GI continuity</td>
</tr>
<tr>
<td></td>
<td>Reoperative pelvis</td>
<td>No ostomy</td>
</tr>
<tr>
<td>APR</td>
<td>At-risk colon</td>
<td>No reoperative</td>
</tr>
<tr>
<td></td>
<td>Permanent ostomy</td>
<td>pelvis</td>
</tr>
<tr>
<td>TPC w/Ileostomy</td>
<td>Ileostomy (watery)</td>
<td>No at-risk colon</td>
</tr>
<tr>
<td>IPAA</td>
<td>Infertility (young women)</td>
<td>Intact GI continuity</td>
</tr>
<tr>
<td></td>
<td>Liquid BMs</td>
<td>No at-risk colon</td>
</tr>
</tbody>
</table>

1. Low anterior resection (LAR) with restoration of GI continuity.
2. Abdominal perineal resection (APR) with colostomy.
3. TPC with ileostomy.
4. TPC with ileoanal J pouch (IPAA) reconstruction.

In general, most patients want restoration of GI continuity, so that makes either an LAR or IPAA preferable to most affected individuals. The APR is reserved for patients with a rectal cancer invading the sphincter complex or a patient with poor sphincter function (preexisting difficulty controlling BMs). Men older than 70 and women older than 65 generally do not have good pouch function, so an IPAA is generally not offered in these age groups. The TPC with ileostomy is reserved for the patients with a rectal cancer invading the sphincter and a synchronous colon cancer, patients with poor sphincter function and synchronous cancers, or patients who do not mind an ostomy and desire maximum risk reduction.

**Summary HNPCC**

Making the diagnosis of Lynch syndrome requires a high index of suspicion and careful decision making regarding which testing to order. Germline testing can be expensive and is often unrevealing. Using the Amsterdam criteria to identify at-risk patients and then doing microsatellite instability (MSI) testing and IHC staining on the tumor cells and normal tissue can further narrow the population that needs germline testing. For patients with HNPCC and a new colon cancer and good anal sphincter function, a TAC
with an ileorectal anastomosis is the preferred operation as it maximizes risk reduction and minimizes at-risk colon to screen. For HNPCC patients with rectal cancer there are several options, depending on sphincter function, location of tumor, patient’s age, and the desire for restoration of GI continuity versus risk reduction. These are personal decisions, and the counsel of a surgeon experienced with caring for patients with the combination of HNPCC and rectal cancer can be very helpful in making the right surgical decision. For Lynch syndrome patients who have not had a colectomy, a yearly colonoscopy is recommended, and every 3 years an EGD. For women of childbearing age, yearly gynecologic exams with transvaginal ultrasound and endometrial biopsy ± CA-125 is also recommended. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) is recommended for all women who have completed childbearing.

OTHER POLYPOSIS SYNDROMES

Colon Cancer Syndrome X

Patients with genetic syndromes that increase their predisposition for developing colorectal cancers will benefit from having their syndromes better understood. The more that is known, the more likely that appropriate strategies for screening, counseling, and treatment for those patients and their relatives can be delivered. One genetic syndrome that is becoming better understood is HNPCC. Although these patients, similar to the majority of patients who develop colorectal cancers, develop adenomas as precursors to adenocarcinomas, they were named as nonpolyposis to contrast to them to familial syndromes where patients develop multitudes, often a hundred or more, polyps, such as FAP. Patients with HNPCC are defined by what is known as the Amsterdam criteria. The Amsterdam criteria is based on family history and requires that at least three family members are affected by colorectal cancer over two or more generations, with one being a first generation relative of the other two and at least one individual diagnosed before the age of 50. There are subtypes of the Amsterdam criteria that depend on whether there are extracolonic manifestations or not. Amsterdam criteria one (AC1) involves all family members having colorectal cancer,
while Amsterdam criteria two (AC2) includes families with extracolonic cancers, such as endometrial and uroepithelial cancers.\textsuperscript{73,74} It has been shown that a subgroup of families with HNPCC had genetic mutations in defined set of mismatch repair genes, and this cohort is referred to as Lynch syndrome. Another subset of families, who met the Amsterdam criteria but did not have any of these mutations in the mismatch repair genes, have been named as having colon cancer syndrome X.\textsuperscript{72,75}

Less is known about colon cancer syndrome X than Lynch syndrome, but there appear to be differences between the two syndromes that may influence screening and management strategies for affected families and perhaps improve our understanding of colorectal cancer pathogenesis overall. The incidence of patients with colon cancer syndrome X, while not clearly defined, is estimated to be 2\% to 4\% of all colorectal cancers.\textsuperscript{76,77} The patients with colon cancer syndrome X do not have mutations in the mismatch repair genes shown to harbor mutations in patients with Lynch syndrome. Early studies show that mutations that might be involved in colon cancer syndrome X include genes such as ZRANB1, CDC27, CENPE, CTBP2, IRF5, and BTNL2 that truncate proteins involved in cell shape, motility, mitosis, transcription, and immune response. These mutations may or may not be the cause. The complexity is heightened by the potential lack of penetrance in colon cancer syndrome X to begin with.\textsuperscript{78,79} As of yet, there is no genetic testing to identify patients with colon cancer syndrome X.

Histopathologically, tumors from patients with colon cancer syndrome X differ from patients with Lynch syndrome. The tumors are more likely to be moderately differentiated rather than poorly differentiated. They are more likely to harbor a tubular architecture and have serrated projections. They also have less mucin production and presence of tumor-infiltrating lymphocytes.\textsuperscript{80} A lack of clear similarity in the histopathology, however, has been noted. This lack of a distinctive morphology has led to the recommendation that a diagnosis of colon cancer syndrome X should involve morphology with a family history.\textsuperscript{81}

Clinically, patients with colon cancer syndrome X are different than patients with Lynch syndrome. They tend to be a bit older at diagnosis, with an average age of 57 at presentation, harbor more left-sided tumors, have a slower progression from adenoma to adenocarcinoma, and have less risk of non-colorectal cancers.\textsuperscript{75,81} Recommendations for surveillance colonoscopies
still begin at 5 to 10 years younger than the age at which any affected family member was diagnosed but allow for an interval of a follow-up colonoscopy of every 3 to 5 years.  

In summary, colon cancer syndrome X is found in patients who meet the Amsterdam II criteria but have no identifiable genetic mutation in an MMR gene. These patients have a predilection for colon and rectal cancer but not the other cancers associated with HNPCC. Surgical management of their colonic disease mirrors management for patients with Lynch syndrome.

Juvenile Polyposis

Juvenile polyposis syndrome is a rare (1:100,000 births) autosomal dominant syndrome that leads to the development of polyps in the colon and rectum. Although it is a genetic syndrome, a family history is only found in 20% to 50% of cases, implying that many patients are the first in their families to acquire the mutation responsible for the syndrome. Mutations that have been identified include a mutation in the SMAD-4 tumor suppressor gene on chromosome 18q21 or in the BMPR1-A gene on chromosome 10q23. The syndrome is characterized by the development of multiple hamartomatous polyps in the gastrointestinal tract. Although patients typically develop between 50 and 200 polyps, you only need one polyp plus a family history to be diagnosed with the syndrome. Patients can present with anemia or rectal bleeding from the polyps or pain from prolapsed polyps. Histologically, the polyps contain no smooth muscle and can detach from the bowel wall and pass per anus. If they are noted on colonoscopy, however, they should be removed, as they can contain adenomatous dysplasia and progress to adenocarcinoma. Patients have a 30% to 50% cumulative lifetime risk of developing colorectal carcinoma, a 13.7% risk of developing gastric cancer, a 10% to 20% risk of developing cancer in the upper GI tract, a 3.4% risk of developing duodenal, and a 3.4% risk of developing pancreatic cancer. Surveillance is recommended to define the extent of the polyposis and remove the polyps. Patients begin receiving screening colonoscopies and esophagogastroduodenoscopies by age 15 or at the time of diagnosis. The screening continues every year until the polyps are cleared and is then repeated every 2 to 3 years thereafter. If the polyps are too numerous to clear or too large to be removed endoscopically, patients may require a TAC
with an ileorectal anastomosis or a TPC with a restorative IPAA.

**Peutz-Jeghers Polyposis**

Peutz-Jeghers syndrome is a rare (1:120,000-200,000 births) autosomal dominant syndrome with variable to high penetrance that leads to the development of polyps within the colon and rectum. Seventy percent of patients with Peutz-Jeghers syndrome have a mutation of the serine threonine kinase gene, STK11/LKB1. The syndrome is characterized by the development of multiple hamartomatous polyps in the gastrointestinal tract, most commonly in the small bowel and colon and rectum. Less commonly, patients can develop polyps in the stomach or urinary tract. The polyps can range in size from 0.5 cm to 5 cm and can develop adenomatous changes progressing to adenocarcinoma.¹⁹

Most visibly, patients with Peutz-Jeghers syndrome will develop mucocutaneous pigmentation in locations including the lips, buccal mucosa, eyes, nostrils, hands, and feet. This pigmentation occurs in infancy but fades by late adolescence or adulthood. The presence of the pigmentation allows patients to be identified for screening. These patients may be asymptomatic. The polyps, however, can lead to clinical presentation of symptoms of blood loss, anemia, and/or obstruction from bleeding or intussusception.⁸⁶ Patients have risks of developing malignancy in the polyps or other associated malignancies as well as the risks incurred from benign polyps that result in clinical scenarios resulting in multiple operations. The cancers occur in the breast (lifetime risk of 54%), colon and rectum (20%-39%), pancreas (30%-36%), small bowel, stomach (5%), esophagus, uterus, ovary, testicle, and lung.⁸⁷ Repeated laparotomies and bowel resections for bleeding and/or intussuscepting polyps can lead to short bowel or problematic adhesions. Surveillance strategies are designed to find lesions that are likely to become emergently symptomatic or are precursors to malignancy. To address the lesions within the small bowel, at age 8 to 10 patients undergo baseline EGD, barium studies, and capsule endoscopies, and repeat these studies every 2 to 3 years if they are revealing. If no small bowel polyps are seen, further studies are deferred until age 18, when they are resumed along with colonoscopies to address polyps within the colon and rectum. These studies are repeated every 2 to 3 years.⁸⁸,⁸⁹ If at any point symptomatic polyps or asymptomatic polyps
greater than 1.5 cm in size are noted, they are removed. This can be done endoscopically or via combined laparotomy/laparoscopy with on-table enteroscopy or enterotomy. As these patients are at risk for extracolonic malignancies they are also screened for breast, testicular, pancreatic, uterine, and ovarian cancer with appropriate physical examinations, imaging, tumor marker, and genetic testing.

Cowden Syndrome

Cowden syndrome is a rare (1:200,000-250,000 births) autosomal dominant polyposis syndrome. The mutation that leads to this syndrome is in the PTEN gene, which interestingly is the same gene that is mutated in the phenotypically different Bannayan-Riley-Ruvalcaba syndrome. Patients with Cowden syndrome develop polyps in the colon and rectum 30% to 90% of the time, for which there is a risk of development into adenocarcinoma. The rarity of this disease has made it difficult to truly understand the risk of developing colorectal cancer and hence produce colonoscopic screening guidelines. Most authors, however, recommend that colonoscopic screening begin between the ages of 35 to 45 and proceed at a frequency determined by the degree of polyposis found at the scope. Patients with Cowden syndrome also develop hamartomas in their mouth, leading to a nodular-appearing buccal mucosa, and elsewhere in their GI tracts. These patients are also at risk for macrocephaly, trichilemmomas, and benign and malignant neoplasms of thyroid, breast, uterus, and skin.

Bannayan-Riley-Ruvalcaba Syndrome

Bannayan-Riley-Ruvalcaba syndrome is a rare autosomal dominant polyposis syndrome. The mutation that leads to this syndrome is in the PTEN gene, which interestingly is the same gene that is mutated in the phenotypically different Cowden syndrome. Patients with Bannayan-Riley-Ruvalcaba syndrome develop juvenile polyps 50% of the time. They are also at risk for developing pigmented macules on the penis, macrocephaly, intellectual disabilities, lipomatoses, and hemangiomas. The risk of developing colorectal cancer is unclear, thus screening recommendations are not standardized.
Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is a very rare polyposis syndrome with no evidence of inheritance. In adulthood, these patients develop gastrointestinal hamartomas. The polyps are located predominantly in the duodenum, additional segments of the small bowel and the stomach. The polyps can develop adenomatous changes and there is a 10% risk of developing adenocarcinoma. The mucosa of the stomach can be abnormal, leading to malabsorption, protein loss, and hypokalemia. In addition, these patients are at risk to develop alopecia, onychodystrophy, and hyperpigmentation of the skin of the face and eyelids.

CONCLUSION

Polyposis syndromes are a variable group of genetic diseases that account for a small but measurable number of patients with colorectal cancer as well as other associated extracolonic neoplasms. Most are autosomal dominant but a few recessive variants exist. Known kindreds should be enrolled in a genetic registry, and a formal screening plan should be in place for all affected family members. Unaffected family members can be screened for colorectal cancer as a normal person in the population at large. Furthermore, a high index of suspicion in patients with a strong family history of cancer may identify new undiagnosed kindreds that can then lead to a screening program for that extended family. This has the potential to prevent many cancers or manage those diagnosed at an early and curable stage.

REFERENCES

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Jenkins MA, Hayashi S, O’Shea AM, et al. Pathology features in Bethesda guidelines predict


INTRODUCTION

Tumor is a descriptive term for a growth or mass of cells that are independent of the physiologic function or demand of their surrounding structures. The 2 characteristic biologic growth patterns of tumors include the ability to (1) disrespect tissue boundaries and invade other structures (invasiveness) and (2) gain access to blood and lymph vessels or other structures to spread tumor cells to distant locations and allow these specially equipped cells to survive and grow new remote tumors (metastases). If a tumor does not have either property, it is benign; if a tumor can invade locally but even at a large size does not have a tendency to metastasize, it is called semimalignant; and if a tumor has the ability to metastasize once a sufficient size is reached, it is a malignant tumor.

Colorectal lesions may be classified as benign, potentially malignant, or malignant based on their pathologic features (Table 49-1); the semimalignant variant with invasion only but no affinity to later form of metastases is not common in the colon. The overwhelming majority of colorectal tumors are of epithelial origin and arise from the mucosal surface, where they become visible descriptively as a polyp. Benign polyps include nonneoplastic polyps
(eg, hyperplastic, hamartomatous, or inflammatory polyps); the potentially malignant group consists of adenomatous polyps. Once dysplastic cells in a polyp cross the boundaries of the mucosa (basement membrane and muscularis mucosae) and start to invade the submucosa and the muscularis mucosae, a true cancer (carcinoma) with the potential to metastasize is established. Tumors of nonepithelial or mesenchymal origin are comparably rare and include, among others, lipoma, lymphoma, carcinoid, and sarcoma.1-3

**TABLE 49-1: INTRODUCTION: CLASSIFICATION OF COLON TUMORS**

**A. Epithelial Tumors of the Colon**

<table>
<thead>
<tr>
<th>Type</th>
<th>Class</th>
<th>Subclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesions</td>
<td>Hyperplastic polyps</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Noninherited gastrointestinal polyposis syndromes</td>
<td>Hyperplastic polyposis</td>
</tr>
<tr>
<td></td>
<td>Hamartomas</td>
<td>Juvenile polyps</td>
</tr>
<tr>
<td></td>
<td>Inflammatory polyps</td>
<td>Cowden syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bannayan-Riley-Ruvalcaba syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cronkite-Canada syndrome</td>
</tr>
<tr>
<td>Potentially malignant</td>
<td>Adenomatous polyps</td>
<td>Sporadic colon cancers</td>
</tr>
<tr>
<td>lesions/syndromes</td>
<td>Hereditary adenomatous polyposis syndromes</td>
<td>Hereditary colon cancers</td>
</tr>
<tr>
<td></td>
<td>Noninherited gastrointestinal polyposis syndromes</td>
<td>Familial adenomatous polyposis (FAP)</td>
</tr>
<tr>
<td></td>
<td>Inherited hamartomatous polyposis syndromes</td>
<td>Attenuated familial adenomatous polyposis (AFAP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cronkite-Canada syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Juvenile polyposis syndromes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peutz-Jeghers syndrome</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>Epithelial tumors of the colon</td>
<td>Sporadic colon cancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial colorectal cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hereditary nonpolyposis colon cancers (HNPPCC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial/hereditary polyposis coli cancers</td>
</tr>
</tbody>
</table>

**B. Nonepithelial Tumors of the Colon**

<table>
<thead>
<tr>
<th>Type</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesions</td>
<td>Lipomas and lipomatous polyposis</td>
</tr>
<tr>
<td>Potentially malignant</td>
<td>Carcinoid/neuroendocrine tumors</td>
</tr>
<tr>
<td>lesions/syndromes</td>
<td>Gastrointestinal stromal tumors (GISTS)</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>Nodular lymphoid hyperplasia of the colon</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

**C. Secondary Tumors to the Colon**

<table>
<thead>
<tr>
<th>Type</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesions</td>
<td>Endometriosis</td>
</tr>
<tr>
<td>Potentially malignant</td>
<td>Leukemia</td>
</tr>
<tr>
<td>lesions/syndromes</td>
<td>Endometriosis transforming to cancer</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td>Carcinomas from other primary sites</td>
</tr>
</tbody>
</table>
Colonic tumors are important for 2 reasons. First, they are frequent and account for both a significant mortality rate as well as high cumulative health care costs. Second, the sequence of events leading from a normal mucosa to a manifest cancer occurs through largely preventable precursor stages over the course of several years. Thus, this chapter predominantly focuses on the detection, management, and prevention of these conditions.

**EPIDEMIOLOGY**

Colorectal cancer is the most common malignancy in the gastrointestinal tract. In the United States, colorectal cancer is the third leading cause of cancer death in both men and women and the second leading cause of cancer death when men and women are combined. With an estimated 134,490 newly diagnosed cases, this disease will be responsible for an estimated 49,290 deaths in the year 2016. The lifetime risk of approximately 6% in our Western civilization means that 1 in 18 individuals of the general population will be affected by colorectal cancer and many more by polyps, making it an important public health issue. Worldwide, colorectal cancer shows large geographical differences, with a crude incidence of 6.5 and 7.7 cases per 100,000 females and males, respectively, in less developed areas as opposed to 50.9 and 60.8 cases, respectively, in more developed regions. Regardless of ethnicity, there is an age-dependent increase in incidence with each decade starting at age of 40 years, and the mean age at presentation is around 70 to 75 years.

In the period between 1975 and 2006, the Surveillance, Epidemiology, and End Results (SEER) Registry of the National Cancer Institute (NCI) showed a gradual decline in all cases of colorectal cancer in the United States from 69.7 to 50.6 cases per 100,000. However, although these numbers reflect the trend in whites, the incidence of colorectal cancer in the United States for African Americans has remained at the same level of 59.3 to 61.5 cases per 100,000 individuals. African American males therefore now represent the ethnic subgroup with the highest risk.

**RISK FACTORS, PREVENTION, AND SCREENING**
The specific cause of colorectal cancer is not known. However, a number of genetic and environmental risk factors have been associated with the disease. From a practical and screening standpoint, it has been helpful to group individuals into 3 risk categories (ie, average risk, increased risk, and high risk) based on their presumptive genetic profile as reflected in their individual and family history. The high-risk and increased-risk groups consist of patients with known hereditary syndromes or bowel diseases or patients with a personal or family history of polyps or cancer, all of which are discussed in a later section of the chapter (Table 49-2).

| TABLE 49-2: COMPARISON OF MAJOR RISK CATEGORIES |
|----------------|----------------|----------------|----------------|
| Variants       | ACCP, Gardner, Turcotte | Lynch I/II     | Ulcerative colitis, Crohn's disease |
| Genetics       | Chromosomal deletions, K-ras, DCC, p53, APC | + Autosomal dominant APC | + Autosomal dominant MSH2, MLH1, PMS1/2, MSH6 |
| Age of onset   | >40 y<br>Average 70-75 | Polyps start after age 10-20, cancer in 100% at age 40 | <50 y<br>Any, often young patients |
| Number of polyps | Variable, <10 | >100 | <10<br>Depending on age at onset, duration of disease, extent of active disease |
| Risk           | 5%-6% of population | 100% | >80%<br>Active disease |
| Location       | Left > right colon<br>NSAID? vitamins? calcium? | Any location<br>NSAID | Right > left colon<br>Active disease |
| Chemoprevention | >50 y (45 y in African Americans) | Genetic counseling | >25 or 10-15 y before cancer onset in youngest family member<br>Genetic counseling | 7 y after onset, annually<br>Extracolonic disease |
| Associated risks | Desmoids | Endometrium and other cancers | Extracolonic disease |

Abbreviations: ACCP, attenuated FAP; FAP, familial polyposis syndromes; HNPCC, hereditary nonpolyposis colon cancer; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drug; SCC, sporadic colon cancer.

The majority of cases, however, are sporadic colon cancers that typically arise within a polyp. Geographic and migrational studies have suggested that the Western lifestyle increases the risk for colon cancer, hence suggesting that nutritional and environmental factors may play a key role. A large number of epidemiologic studies have been undertaken to identify these individual, nutritional, lifestyle, genetic, and environmental factors that would either predispose to or prevent the development of colorectal polyps.
and cancer (Table 49-3).¹⁴⁻¹⁹

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic variation</td>
<td>Highest risk in Western countries and lowest in developing countries</td>
</tr>
<tr>
<td>Age</td>
<td>Risk increases sharply after the fifth decade</td>
</tr>
<tr>
<td>Diet</td>
<td>Increased with high total- and animal-fat diets</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Increased with obesity and sedentary lifestyle</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Risk dependent on type and size</td>
</tr>
<tr>
<td>FAP penetrance in gene carriers</td>
<td>100%</td>
</tr>
<tr>
<td>HNPCC penetrance in gene carriers</td>
<td>80%</td>
</tr>
<tr>
<td>Hamartomatous syndromes</td>
<td>Risk increased with Peutz-Jeghers syndrome and juvenile polyposis but not isolated juvenile polyps</td>
</tr>
<tr>
<td>Previous history of colon cancer</td>
<td>Increased risk for recurrent cancer</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>10%-20% after 20 y</td>
</tr>
<tr>
<td>Radiation</td>
<td>Associated with a mucinous histology and poor prognosis</td>
</tr>
<tr>
<td>Ureterosigmoidostomy</td>
<td>100-500 times increased risk at or adjacent to the ureterocolonic anastomosis</td>
</tr>
</tbody>
</table>

Abbreviations: FAP, familial polyposis syndromes; HNPCC, hereditary non-polyposis colon cancer.
Extrinsic Risk Factors

DIETARY FIBER, MEAT, AND FAT

One of the characteristics of a Western diet generally has been the lack of fiber as opposed to the increased amount of meat, total fat, and animal fats.\textsuperscript{20,21} In view of the known geographic differences, with the highest colorectal cancer incidence in industrialized nations,\textsuperscript{6} a high-fat and low-fiber diet generally has been considered a risk factor for the development of colorectal cancer.\textsuperscript{22} This concept gained support from epidemiologic studies\textsuperscript{23} and resulted in common recommendations of high-fiber supplements to increase the stool bulk, dilute toxins, and reduce the colonic transit time and thus the exposure time to fecal carcinogens.\textsuperscript{24-27} More recent prospective trials, however, have questioned the benefit of dietary fiber supplementation in that they were at best inconclusive and did not reduce the incidence of colorectal cancer.\textsuperscript{28,29} However, selected fats such as $n$-3 fatty acids found in fish oils may have a protective effect,\textsuperscript{30} even though a direct effect to the mucosa could not be observed.\textsuperscript{31} Therefore, it could be concluded that the total amount of fats or fibers is of lesser importance than their quality and origin.\textsuperscript{19,20,32} The protective effect of vegetables and fruits\textsuperscript{33,34} may come not only from their fiber content but also from the content of antioxidative and antiproliferative agents, such as isothiocyanates in cruciferous vegetables (eg, broccoli), which may enhance the expression of carcinogen-metabolizing enzymes and induce apoptosis in neoplastic cells.\textsuperscript{16,35}

CALCIUM, VITAMINS, AND MICRONUTRIENTS

Several prospective studies suggested that increased oral calcium and selenium intake may protect from colorectal polyps and cancers,\textsuperscript{36-41} whereas other studies could not verify a significant benefit.\textsuperscript{42} The mechanism by which calcium supplements are thought to reduce the risk of colon cancer is 2-fold. First, calcium can bind bile and fatty acids in the stool to insoluble complexes that are less likely to attack the colonic mucosa, and second, it can interfere directly with the mucosal cells and decrease their proliferative potential on a cellular level.\textsuperscript{23}
Several vitamins were found to have a cancer-protective effect. Vitamins A, C, and E have been shown to have antioxidant activity. Results from interventional studies, however, have remained somewhat disappointing or controversial.\textsuperscript{43,44}

In a study on postmenopausal women, another correlation was found between dietary heme iron and an increased risk of proximal colon cancer, especially in conjunction with alcohol consumption, whereas intake of dietary zinc reduced the risk of both proximal and distal colon cancer.\textsuperscript{45}

**ASPIRIN AND COX-2 INHIBITORS**

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may interfere with the development of colorectal neoplasms by blocking the cyclooxygenase (COX)-dependent prostaglandin pathway.\textsuperscript{46} The targets are the constitutive COX-1, as well as the cytokine-inducible COX-2, which has been found at increased expression levels in both polyps and cancers.\textsuperscript{47} Therefore, several trials have studied these agents (eg, aspirin and sulindac) for the chemoprevention of colorectal cancer both in sporadic polyps and cancers\textsuperscript{48} and in familial adenomatous polyposis (FAP).\textsuperscript{49-51} In both settings, controlled studies have provided contradictory results.\textsuperscript{52} Regular prophylactic medication with low-dose aspirin may reduce the risk of sporadic colorectal cancer.\textsuperscript{48,53} Data from chemoprevention trials in FAP suggest that COX inhibition may delay the onset and number of adenomatous polyps, but it is not yet clear whether it is able to prevent the cancers overall or reduce their respective risk.\textsuperscript{49-51} COX-2–independent mechanisms may play a role in the beneficial effect of some COX-2 inhibitors.\textsuperscript{46} A major concern, however, has been the documented increased risk of serious cardiovascular events with the use of COX-2 inhibitors.\textsuperscript{54,55}

Because data on the benefits remain conflicting, physicians must decide how to use these pharmacologic tools in the management of their patients. Based on the presumed small risks in general and the supporting data on a possible benefit, most physicians would be inclined to err on the side of a potential benefit in preventing colon polyp formation. Low doses of aspirin and calcium may be helpful in preventing polyps and cancers. However, concern about cardiovascular side effects and increased mortality has resulted in a withdrawal of more potent COX-2 inhibitors until further redefinition of
the indications and risk groups has been accomplished.\textsuperscript{54,55}

**CHOLECYSTECTOMY AND BILE ACIDS**

Evidence that bile acids may act as cocarcinogens or tumor promoters comes from both experimental and epidemiologic studies.\textsuperscript{56,57} Bile acids can induce hyperproliferation of the intestinal mucosa via a number of intracellular mechanisms. Cholecystectomy, which alters the enterohepatic cycle of bile acids, has been associated with a moderately increased risk of proximal colon cancers.\textsuperscript{58,59} It cannot be ruled out, however, that it is less the effect of the cholecystectomy than the impact of other, not yet identified factors in the lithogenic bile of such patients. A number of cofactors have been identified that may enhance or neutralize the carcinogenic effects of bile acids, for example, the amount of dietary fat, fiber,\textsuperscript{23} or calcium.\textsuperscript{60} Calcium, in fact, binds bile acids and thus may reduce their negative impact. However, other more intrinsic mucosa-protective mechanisms of calcium supplements probably are more relevant for the demonstrated reduction of recurrent adenomatous colon polyps.

**SMOKING AND ALCOHOL CONSUMPTION**

The risk of colorectal cancer is increased, though modestly, among long-term smokers compared with nonsmokers.\textsuperscript{26,45,61,62} The data suggested a dose-response relationship between pack-years of tobacco use and the development of adenomatous polyps.\textsuperscript{63-66} Equally, excessive alcohol consumption has been associated with an increased risk for colon cancer.\textsuperscript{26,45,61,62}

**OTHER FACTORS**

An ever-increasing number of other factors are accumulating that have been attributed to an increased risk of colon cancer, such as lack of physical activity, diabetes, serum insulin levels, elevated concentrations of insulin-like growth factor 1, and low concentrations of insulin-like growth factor–binding protein 3 (IGFBP-3).\textsuperscript{67} The complexity of interactions between these factors and the previously mentioned parameters, however, makes it difficult at the present time to draw conclusions that have an impact on clinical practice.


**Intrinsic Risk Factors**

**PERSONAL AND FAMILY HISTORY**

There is generally little debate on whether the presence of an adenomatous pathology or chronic inflammatory bowel disease (IBD) in itself represents a risk factor for a subsequent colon cancer. In patients with a colon cancer, synchronous colorectal cancers are found in 5% to 10%, whereas about 10% to 20% of patients with a history of colorectal cancer will develop metachronous primary cancers in the large intestine. A personal history of adenomatous colonic polyps is an indicator for an increased colonic predisposition to develop subsequent adenomatous or cancerous changes.\(^{12,68-72}\)

Compared with the general population, relatives of patients with colon cancer have a 2 to 4 times increased risk of developing the disease themselves (Table 49-4).\(^{26,73,74}\) A similar, even though proportionally lesser, risk is observed for family members of individuals with colonic adenomatous polyps.

<table>
<thead>
<tr>
<th>TABLE 49-4: LIFETIME RISKS OF COLORECTAL CANCER IN FIRST-DEGREE RELATIVES OF PATIENTS WITH COLON CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population risk without risk factors</td>
</tr>
<tr>
<td>One relative affected</td>
</tr>
<tr>
<td>One first-degree relative and one second-degree relative affected</td>
</tr>
<tr>
<td>One relative aged &lt;45 y affected</td>
</tr>
<tr>
<td>Two first-degree relatives affected</td>
</tr>
<tr>
<td>Dominant pedigree</td>
</tr>
</tbody>
</table>


**INFLAMMATORY BOWEL DISEASE**

IBD is a strong risk factor for colorectal cancer. The risk correlates with the age of onset and extent and duration of active disease.\(^{75,76}\) In contrast,
however, the disease activity historically was not thought to be correlated with the risk, but recent studies have challenged this view.\textsuperscript{77} In patients with ulcerative colitis, the risk of colorectal cancer increases from approximately 3\% in the first decade to 10\% to 20\% in the second decade.\textsuperscript{75,76} In patients with Crohn’s disease with colonic involvement, the disease-associated risk for colorectal cancer is also elevated but generally to a lesser extent.\textsuperscript{78-80}

**OTHER FACTORS**

Less frequent risk factors for colorectal cancers may include a history of a ureterocolostomy\textsuperscript{81} or previous radiation treatment.\textsuperscript{82} The former requires the combination of fecal bacteria and urine because the microbes degrade urinary metabolites into strong carcinogens.\textsuperscript{81,83,84} When colonic mucosa is used for bladder augmentation, no increased cancer risk is observed owing to the absence of bacteria. The findings in radiation-induced colorectal cancer are a little less clear, but it has been suggested that it may be associated with a mucinous histology and poor prognosis.\textsuperscript{82}

**Prevention and Screening**

Because symptoms are not reliable for early detection of colorectal cancer, risk-adjusted screening programs for asymptomatic individuals are important. Effective screening has to be based on an understanding of the adenoma-carcinoma sequence, which may take up to 5 to 10 years from the first molecular change to a clinically manifest cancer, and should reflect an individual’s genetic and disease- or age-dependent risk for the development of colorectal cancer.\textsuperscript{11,12,85-87} Any prevention program has to be sensitive but also practical and cost-effective in order to achieve a broad screening of the population at risk. The term “screening” is applicable only to asymptomatic people; if symptoms are present, it is not screening but diagnostic tests that are initiated. Common tools for screening include fecal occult blood tests (FOBTs), flexible sigmoidoscopies or colonoscopies, and contrast enemas or computed tomography (CT) colonography.\textsuperscript{88}

The American Cancer Society, endorsed by the major professional societies, recommends starting colorectal cancer screening in asymptomatic average-risk adults at age 50.\textsuperscript{11,12,85-87} A slightly earlier screening start at age
of 45 has been recommended recently for African American patients based on their statistically significant increased risk. A first baseline colonoscopy is to be performed and, if no pathology is found, repeated every 10 years. In addition, an FOBT should be done on an annual basis, and any positive result should precipitate a full colonic evaluation. Every 5 years, a limited endoscopy (flexible sigmoidoscopy) or barium enema is indicated. If precursor lesions are found, they should be removed, and a colonoscopy should be performed after 1 to 3 years to detect missed (20%) or recurrent polyps.

In individuals at increased risk (eg, personal/family history of polyps or cancer or African American ethnicity) or at high risk (eg, cancer syndromes or IBD), the screening has to start earlier (see Table 49-2) and has to be performed at a higher frequency. Successful screening programs have been shown to reduce the colorectal cancer incidence by 76% to 90%.

PATHOGENESIS OF COLONIC CANCER

Carcinogenesis in the colon is a complex multistep process in which a multitude of alterations must coincide in order to transform a normal cell into a malignant cell. Several categories of genes are involved that normally are regulated in a sophisticated network to keep a tight balance between cell growth and turnover, cell death, DNA replication, and mismatch repair. Disruption of the fine balance between oncogenes, which promote cell proliferation, and tumor suppressor genes, which inhibit excessive growth, results in a growth advantage and allows malignant cells to expand.

Colon Cancer: A Genetic Disease

All cells of even such a complex organism as a human being have DNA that is virtually identical to the DNA found in the zygotes. DNA mutations can occur either as a germline mutation or as a somatic mutation. The former may be transmitted from one to the next generation as an inherited defect. More commonly, a spontaneous mutation occurs in a non-germline cell during the growth, development, and maintenance of a tissue or organ (somatic mutation). Even in the cycle of a normally functioning cell, there is a high chance of spontaneous gene mutations, most of which will not result in a
growth advantage to the harboring cell. Genesis of a cancer therefore requires several independent accidents to occur in 1 cell. One can assume that a normal cell will be able to detect damage to its own DNA and maintain an effective repair mechanism. However, if the cell is too severely damaged, it might rather initiate the inherent suicide program called apoptosis. When a cell fails to recognize or correct DNA damage and continues to replicate, accumulation of faulty gene products within the cell may eventually lead to a proliferative response. If that replication exceeds the growth potential of the neighboring normal cells, the mutation provides a growth advantage that will increase the state of “genetic instability” and hence lead toward a malignant cell. Despite this potential, most mutations are silent or lethal to the cell rather than beneficial in terms of providing the cell a biologic advantage. The triggers and the step-by-step cumulative failures that lead to carcinogenesis still are relatively poorly understood.

Two types of genetic instability may occur: at the chromosome level or at the DNA level. A loss of chromosomal material, that is, a chromosomal instability (CIN), results when the chromosomes are not divided symmetrically during mitosis such that 1 daughter cell receives both copies and the other cell receives none. On an electrophoretic gel, this can be visualized as a loss of 1 or more bands, which is described as loss of heterozygosity (LOH), and has been associated with a worse prognosis in colorectal cancer. The second form of genetic instability, at the DNA level, occurs when replication errors in repetitive short polymorphisms lead to an additional band or bands. This phenomenon is described as microsatellite instability (MSI), and it has been a characteristic feature of hereditary nonpolyposis colon cancers (HNPCCs).

During the process of cell division, DNA is duplicated, with the original DNA serving as a template for the replicated copy. DNA polymerase serves as a “proofreader” that recognizes mismatched genes, halts the DNA synthesis, removes the defective sequence, and then resynthesizes the DNA. Failure of the DNA mismatch repair system predisposes to the development of mutations within daughter cells. Enzymes that monitor newly formed DNA and correct replication errors are called DNA mismatch repair (MMR) systems.

Specific gene functions are lost when both copies (alleles) of a gene are inactivated. Thus, when a germline mutation occurs in a suppressor gene,
only the mutation of the remaining normal allele is required for the gene’s loss of function. When both copies of the gene are normal, 2 mutational events are required for the gene’s loss of function. This 2-hit hypothesis may explain why inherited diseases usually manifest at an earlier age than sporadic disease.5

The Adenoma-Carcinoma Model

After identifying several genetic alterations in colorectal specimens at various stages of their neoplastic transformation and progression, Vogelstein and colleagues in 1988 pioneered a genetic model for colorectal tumorigenesis that since has been known as the adenoma-carcinoma sequence (Fig. 49-1).3 This multistep model described the carcinogenesis as an accumulation of genetic events, uninhibited cell growth, and proliferation and clonal development. Gene mutations and chromosomal/gene losses that were observed in sporadic colon cancer include the APC gene (adenoma–polyposis coli), MMC gene (mutated in colon cancer), K-ras, DCC (deleted in colon cancer), and p53.2,96,97 Mutations of the APC gene, which is involved in the control of cell-to-cell adhesions and intercellular communication, are found in 60% of even small adenomatous polyps, as well as in carcinomas,98 and therefore are believed to occur as a very early event in carcinogenesis.

Mutations of K-ras, which under normal function plays a role in intracellular signal transduction and stimulated cell division, occur in larger adenomas and carcinomas and are thought to stimulate cell growth. Deletion of the tumor suppressor gene DCC may be important in the progression from a benign polyp to a malignant condition.99 Mutations of the p53 gene, which are among the most frequent gene mutations in human cancers, are also common in invasive colon cancers but rare in adenomas, suggesting that p53 mutations occur as a late event in the development of the invasive phenotype.100 The wide range of gene mutations, inactivations, and deletions in the progression to carcinoma seems to hold the secret code for the various tumor behaviors observed in the clinical setting. It is important to note, however, that an increasing number of other genetic events have been observed and reported and that no single event seems to be equally present in all colon cancers. One therefore should caution that the described sequence is only one possible model and that the scenario may not reflect all aspects of colonic
The Cancer Stem Cell Model

Tumors arise from the expansion of a mutated cell and contain a heterogeneous cellular population. There is increasing evidence that not all cells within a tumor have the same capacity for proliferation and tumorigenesis. Instead, tumor growth is driven by a subset of the population, termed cancer stem cells, that have the ability to self-renew and differentiate to form all the lineages found within the tumor. This has implications for future therapeutic treatment as current radiotherapy and chemotherapy target all rapidly dividing cells nonspecifically. If all cancer stem cells within the tumor are not destroyed, this could lead to disease relapse and metastasis.\textsuperscript{101,102}

Cancer stem cells are thought to arise from normal stem cells that have lost their regulation of self-renewal or from progenitor cells with a defined lineage fate that have obtained the ability to self-renew. Normal stem cells are likely targets for transformation because the machinery for self-renewal is already active, and they can persist in normal tissue for a long time and accumulate transforming DNA damage. The intestinal stem cell niche provides a unique environment to regulate self-renewal and differentiation of these stem cells. Multiple signaling pathways are used to regulate stemness within the niche, including the Wnt, BMP, and Hedgehog pathways, and aberrations in these signals can disrupt the normal crypt-villus axis.\textsuperscript{103} Myofibroblasts are thought to play an important role in regulating the microenvironment found within the stem cell niche, in normal tissue, primary tumors, and metastatic lymph node disease.\textsuperscript{104} The centers of tumors often
have a lack of blood supply and oxygen, and there is evidence that hypoxia maintains the niche for colorectal cancer stem cells by maintaining stemness and inhibiting lineage differentiation via BMI1 and Notch1. Various cell surface markers have been identified to enrich for colorectal cancer stem cells, including CD133, CD44, and CD24. It is hoped that treatments that specifically target the cancer stem cell population within a tumor will allow more complete treatment of the disease and prevent relapse.

HEREDITARY AND NONHEREDITARY COLON TUMORS

Nonhereditary Colon Cancer

SPORADIC COLON CANCER

Sporadic colon cancer, that is, colon cancer arising in individuals without a family history or an inherited predisposition, accounts for approximately 60% of all colorectal cancers and affects patients commonly older than 50 years. The risk factors associated with sporadic development of colon cancer have been discussed previously in the epidemiology section of this chapter (see Table 49-3).

FAMILIAL COLON CANCER

Familial colon cancer is the second most common (25%-30%) and, at the same time, least understood pattern of genetic colon cancer development. In affected families, colon cancer develops too frequently to be considered a sporadic colon cancer, but the pattern is not consistent with the known inherited syndromes. An association of familial colon cancer has been found with polymorphisms, which reflect subtle genetic changes in the form of variations in the nucleotide base sequences but which do not affect protein structure. Familial colon cancer in the Ashkenazi Jewish population probably is the result of an APC germline mutation on codon 1307 (I1307K). This mutation, which predisposes to sporadic mutations at distant sites of the gene and later results in structural protein abnormalities, is found in 6% of all Ashkenazi Jews and in 28% of those with both a personal and a family
Hereditary Colon Cancer

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited syndrome with near-complete penetrance. The offspring of affected individuals thus have a 50% risk of inheriting FAP. However, up to 20% of patients with FAP have new mutations without a family history. This condition is attributed to a truncating mutation in the germline adenomatous polyposis coli (APC) gene on chromosome 5q21. Variants of the polyposis syndrome are classified as Gardener syndrome (ie, osteomas, desmoid tumors, thyroid neoplasms, and congenital hypertrophy of the retinal pigment epithelium) and Turcot syndrome (ie, brain tumors).

The inherited syndrome of FAP and its variants accounts for less than 1% of all colon cancers. It is characterized by greater than 100 and often several thousand adenomatous intestinal polyps that start to develop in the late teens and early twenties and turn into cancer by age 40 to 45. An attenuated variant of the disease is relatively rare and is characterized by a lower number and a later onset of both the polyps and the resulting cancer (see the following text). Nearly all FAP patients develop duodenal adenomas that are severe in 10% and account for the group’s second highest cancer risk, with adenocarcinoma developing in the periampullary region in 3% to 10% of patients. Carcinoma arising in the antrum and duodenum after colectomy is the main cause of cancer-related deaths in FAP patients. Nonadenomatous fundic gastric polyps develop in approximately 10% to 30% of patients with FAP but usually do not have a malignant potential. Ten percent of FAP patients develop desmoid tumors either intra-abdominally or on the abdominal wall, extremities, and trunk. Histologically, desmoids are fibromatous lesions consisting of large proliferation of myofibroblasts. Even though they do not necessarily carry features of a malignant lesion, the recent literature suggests a low-grade sarcoma-like behavior. Desmoids are lethal in 10% and are the third most frequent cause for mortality of FAP patients, mainly due to the intra-abdominal variants, which cause small bowel and ureteral obstructions.
Approximately 25% of FAP patients remain without an identified APC mutation (APC negative),\textsuperscript{116,117} and using a detailed analysis, they seem to differ in terms of lower polyp number, later age at diagnosis, and lower occurrence of extracolonic manifestations as compared with classic FAP patients.\textsuperscript{114,118} This variant of FAP is known as \textit{attenuated familial adenomatous polyposis} (AFAP).

**HEREDITARY NONPOLYPOYSIS COLON CANCERS**

\textit{Hereditary nonpolyposis colon cancer} (HNPCC), also known as \textit{Lynch I} and \textit{II syndromes}, is an inherited autosomal dominant disease that accounts for 3\% to 5\% of all colorectal cancers.\textsuperscript{119} It is characterized by an early onset of colorectal cancers predominantly but not exclusively on the right side of the colon with synchronous and metachronous cancers. Despite its name, these cancers typically arise from colonic polyps, but a diffuse polyposis is not present. The penetrance of the HNPCC predisposition is high and results in an 80\% to 85\% lifetime risk of colorectal cancer and a 40\% to 50\% risk of endometrial cancer.\textsuperscript{115,120,121} Furthermore, HNPCC patients are at increased risk of developing extracolonic malignancies, such as cancer of the small bowel, stomach, hepatobiliary tract, urinary tract, ovary, and brain. The Lynch variants describe patients with predominantly colorectal cancer at a young age (Lynch I) and those with both colorectal and extracolonic cancers (Lynch II).\textsuperscript{119}

An initial observation of expansions and contractions of microsatellite DNA in the genome of colorectal tumor specimens from HNPCC patients established a link between HNPCC and the DNA MMR system.\textsuperscript{122-124} In contrast to the gatekeeper concept applicable to the \textit{APC} gene in FAP, the DNA MMR genes belong to the so-called caretakers, which, when inactivated, do not promote tumorigenesis directly but rather lead to a genetic instability that then promotes tumor growth indirectly.\textsuperscript{125}

To facilitate the clinical diagnosis of HNPCC, the International Collaborative Group on HNPCC (ICG-HNPCC) proposed the Amsterdam Criteria in 1990.\textsuperscript{119} Linkage studies in HNPCC families fulfilling Amsterdam Criteria I (Table 49-5) led to the discovery of the first 2 human MMR genes—\textit{hMSH2} and \textit{hMLH1}. These genes accounted for 45\% to 86\% of all classic HNPCC families.\textsuperscript{126} There also was a higher risk for \textit{hMSH2} mutation
carriers to develop extracolonic cancers, in particular endometrial cancer, as compared with $hMLH1$ mutation carriers.\textsuperscript{121,127} Several other MMR genes have been identified in conjunction with HNPCC and include $hPMS1$, $hPMS2$, and $hMSH6$. A recent study reported that endometrial cancer represents the most common clinical manifestation of HNPCC among female $hMSH6$ mutation carriers and that colorectal cancer cannot be considered an obligate requisite to define HNPCC.\textsuperscript{128} The ICG-HNPCC therefore revised the criteria (Amsterdam Criteria II), which now better weigh extracolonic manifestations (eg, endometrial, breast, small bowel, and upper renal tract cancers) as part of the family history (see Table 49-5). In addition, the less restrictive revised Bethesda Criteria (Table 49-6) were adopted to better serve patients who carry $hMSH2$ or $hMLH1$ gene mutations but otherwise do not fulfill the Amsterdam Criteria. Testing for MSI has become a valuable diagnostic tool to identify individuals with suspected HNPCC because 85\% to 90\% of HNPCC tumors have MSI as opposed to only 15\% to 20\% of sporadic colon cancers.\textsuperscript{95}

**TABLE 49-5: AMSTERDAM CRITERIA I AND II**
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 3 relatives with colorectal cancer, 1 of whom should be a first-degree relative of the other 2.</td>
<td>There should be at least 3 relatives with HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, and ureter), 1 of whom should be a first-degree relative of the other 2.</td>
</tr>
<tr>
<td>At least 2 successive generations should be affected.</td>
<td>At least 2 successive generations should be affected.</td>
</tr>
<tr>
<td>At least 1 colorectal cancer should be diagnosed before the age 50 y.</td>
<td>At least 1 colorectal cancer should be diagnosed before the age 50 y.</td>
</tr>
<tr>
<td>FAP should be excluded.</td>
<td>FAP should be excluded.</td>
</tr>
<tr>
<td>Tumors should be verified by a pathologist.</td>
<td>Tumors should be verified by a pathologist.</td>
</tr>
</tbody>
</table>

Benign tumors, by definition, do not invade adjacent tissue borders, nor do they metastasize to distal sites. By contrast, malignant tumors have the added property of invading contiguous tissues and metastasizing to distant sites.

A polyp is defined as a mass that protrudes into the lumen of the colon. They are subdivided according to the attachment to the bowel wall (eg, sessile or pedunculated), their histologic appearance (eg, hyperplastic or adenomas), and their neoplastic potential (ie, benign or malignant).

Abbreviations: FAP, familial polyposis syndromes; HNPCC, hereditary non-polyposis colon cancer.
Data from Vassen HFA: Clinical diagnosis and management of hereditary colorectal cancer syndromes, J Clin Oncol 2000 Nov 1;18(21 Suppl):818-92S.


TABLE 49-6: REVISED BETHESDA GUIDELINES (2002) FOR TESTING COLORECTAL TUMORS FOR MSI

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer diagnosed in a patient age &lt;50 y</td>
<td>Stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain, sebaceous gland adenomas and keratoacanthomas, and small bowel</td>
</tr>
<tr>
<td>Presence of synchronous, metachronous colorectal cancer, or other HNPCC-associated tumor, regardless of age</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer with MSI-high histology diagnosed in a patient age &lt;60 y</td>
<td>Tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern</td>
</tr>
<tr>
<td>Colorectal cancer diagnosed in at least 1 first-degree relative with an HNPCC-related tumor diagnosed under age 50</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors, regardless of age</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HNPCC, hereditary nonpolyposis colon cancer; MSI, microsatellite instability.


HAMARTOMATOUS POLYPOSIS SYNDROMES

Approximately 4% of colonic cancers are seen in the context of rare syndromes. Among these are inherited hamartomatous polyposis syndromes that are characterized by the presence of gastrointestinal hamartomatous
polyps and an increased risk of gastrointestinal malignancy. Hamartomas result from a disordered differentiation during embryonic development and are characterized morphologically by disrupted representations of normal tissue components.

**Peutz-Jeghers Syndrome.** Peutz-Jeghers syndrome is the second most common hamartomatous syndrome, occurring as an autosomal dominant condition with variable penetrance. Genetic alterations in the \textit{LKB1/STK} (19p13) gene are responsible for approximately 50% of the cases of Peutz-Jeghers syndrome.\textsuperscript{129} The syndrome is associated with hamartomatous polyps of the gastrointestinal tract and cutaneous melanin deposition. The most common location of Peutz-Jeghers polyps is in the upper gastrointestinal tract, specifically the upper jejunum. One of the most characteristic features is the melanin depositions, which are seen most frequently in the perioral region or buccal mucosa but also can occur in the genital region and on the hands and the feet. While a majority of these patients remain relatively asymptomatic, some may present with abdominal pain secondary to obstruction or impending obstruction due to an intussuscepted polyp and others with gastrointestinal bleeding. Patients with Peutz-Jeghers syndrome have a moderately increased risk in the range of 2% to 3% to develop gastrointestinal malignancies and extraintestinal malignancies.

**Juvenile Polyposis Syndrome.** Juvenile polyposis syndrome is the most common hamartomatous syndrome and is inherited as an autosomal dominant trait. The average age of onset is approximately 18 years, and there is an association with congenital birth defects in 15% of patients.\textsuperscript{130} Although the diagnostic criteria for juvenile polyposis syndrome are somewhat controversial, the most commonly used criteria include 3 or more juvenile polyps of the colon, polyposis involving the entire gastrointestinal tract, or any number of polyps in a member of a family with a known history of juvenile polyps.\textsuperscript{131}

In infancy, patients may present with acute or chronic gastrointestinal bleeding, intussusception, rectal prolapse, or a protein-losing enteropathy. In adulthood, patients commonly present with either acute or chronic gastrointestinal blood loss. Most of these patients will be found to have polyps, which are located most frequently in the rectosigmoid region. A germline mutation in the \textit{SMAD-4} gene (18q21) accounts for
approximately 50% of the reported cases of the syndrome. A significant risk of colorectal cancer is associated with juvenile polyposis syndrome, and this syndrome should not be confused with isolated juvenile polyps because the latter have virtually no malignant potential.

**Cowden Disease.** Cowden disease, first described in 1963, is known as multiple hamartoma-neoplasia syndrome. It is an autosomal dominant condition with nearly complete penetrance by age 20 that is caused by germline mutations in the *PTEN* tumor suppressor gene located at 10q22. Cowden disease is unique among the hamartomatous syndromes because polyps arise more commonly from ectodermal rather than endodermal elements. Eighty percent of patients present with trichilemmoma, a benign tumor of the hair shaft. The central nervous system is the second most involved system, with approximately 40% of affected individuals suffering from macrocephaly. Only 35% of patients who meet the diagnostic criteria for Cowden disease have gastrointestinal polyposis, but no increased risk of invasive gastrointestinal malignancy has been reported to date. The majority of patients with Cowden disease suffer from benign thyroid or breast disease, in addition to a projected lifetime risk of 10% for thyroid cancer and of 30% to 50% for breast cancer.

**Bannayan-Riley-Ruvalcaba Syndrome.** Formerly known as its subentity, the Ruvalcaba-Myhre-Smith syndrome, this rare autosomal dominant condition includes 2 other syndromes, both of which, like Cowden disease, are associated with genetic alterations in the *PTEN* gene on chromosome 10q23 and may be considered a variant of juvenile polyposis coli. It is characterized by hamartomatous polyps of the gastrointestinal tract, macrocephaly, mental retardation, delayed psychomotor development, lipid storage myopathy, Hashimoto thyroiditis, and hyperpigmentation of the skin of the penis. No increased risk of colorectal carcinoma, other gastrointestinal malignancies, or extraintestinal malignancy has been documented in these patients.

**Cronkite-Canada Syndrome.** Cronkite-Canada syndrome is characterized by diffuse polyposis and ectodermal abnormalities such as alopecia, onychodystrophy, and skin hyperpigmentation. The syndrome can be distinguished by the diffuse distribution of polyps throughout the entire
gastrointestinal tract with exception of the esophagus, which is spared.\textsuperscript{138} Symptoms include diarrhea, weight loss, nausea, vomiting, and anorexia, as well as paresthesias, seizures, and tetany related to electrolyte abnormalities. Cancer occurs in the stomach, colon, and rectum, but it remains controversial whether polyps in Cronkite-Canada syndrome possess malignant potential. As many as 15\% of patients with Cronkite-Canada syndrome have a malignant tumor at the time of diagnosis.

**PATHOLOGY AND STAGING**

**Polyps**

*Polyp* is a descriptive clinical term for any mucosal elevation. Polyps are further categorized along several dimensions, including

1. Size
2. Character of their attachment to the bowel wall (eg, sessile or pedunculated)
3. Cellular architecture (eg, adenomas, hyperplastic, hamartomas, inflammatory) and histologic appearance (eg, tubulous, tubulovillous, villous)
4. Progression from benign to malignant behavior (eg, benign, dysplastic, cancer)

Most polyps are neoplastic but not necessarily malignancies. Neoplastic polyps consist of cells with the potential to acquire over time the ability to invade and to spread, that is, metastasize. *Dysplasia* is a term used to describe the intervening state between normal tissue and invasive malignancy.

**POLYP SIZE**

The most immediate way in which a polyp can be described is by its size. Intuitively, polyps with a larger mass have a greater volume of neoplastic cells, and hence a higher likelihood of harboring cancer. The relationship between adenomatous polyp size and the presence of invasive malignancy was analyzed elegantly by Nusko et al\textsuperscript{139} (Table 49-7).
TABLE 49-7: RISK OF INVASIVE CARCINOMA IN ADENOMATOUS POLYPS

<table>
<thead>
<tr>
<th>Polyp Size (mm)</th>
<th>Number</th>
<th>% With Invasive Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>5137</td>
<td>0</td>
</tr>
<tr>
<td>6-15</td>
<td>3581</td>
<td>2.2</td>
</tr>
<tr>
<td>16-25</td>
<td>1069</td>
<td>18.6</td>
</tr>
<tr>
<td>16-36</td>
<td>516</td>
<td>42.8</td>
</tr>
<tr>
<td>37-42</td>
<td>219</td>
<td>63.9</td>
</tr>
<tr>
<td>&gt;42</td>
<td>677</td>
<td>78.9</td>
</tr>
</tbody>
</table>


**POLYP ATTACHMENT TO BOWEL WALL**

Polyps of any size or architecture may be pedunculated, sessile, or some combination of both. The main clinical relevance of this distinction lies in the ease of endoscopic removal, with pedunculated polyps being clearly more amenable to removal without surgical intervention.\(^{140,141}\)

It is important to note that the way in which a polyp is attached to the wall of the colorectum does not accurately predict the presence versus absence of an invasive malignancy. Malignant polyps of the colon can be either pedunculated or sessile. The type of treatment that should be offered to a patient depends much more on the other characteristics of the polyp.

**POLYP ARCHITECTURE**

Based on their histologic structure, polyps can be categorized into adenomatous and nonadenomatous polyps, the latter of which consists of hyperplastic, hamartomatous, and inflammatory polyps.

**Adenomatous Polyps (Adenomas).** The most common type of polyp in the colon is the adenomatous polyp. Adenomatous polyps are categorized as tubular, tubulovillous, or villous based on the extent to which the dysplastic epithelium is organized with the normal-appearing tubular architecture.\(^{142}\)
Tubular adenomas are defined by the presence of tubules within 80% or more of the lesion; adenomas with less than 20% showing a tubular configuration are villous lesions; and the remainder is considered tubulovillous. The majority of polyps are tubular (87%), with a minority being either tubulovillous (8%) or villous (5%).

With few exceptions, the treatment for an adenomatous polyp is endoscopic polypectomy. Colorectal cancer screening programs that include colonoscopy with polypectomy have demonstrated a reduction in the incidence of colorectal cancer and colorectal cancer mortality. It is difficult, however, to estimate the likelihood that a small adenoma will progress to a dysplastic adenoma and eventually into cancer. A number of biologic and molecular markers have been analyzed as predictors of a malignant potential, but these are not widely used. Longitudinal and comparative data suggest that polyps not only progress but also may regress. Despite these vagaries, any adenomatous polyp should be considered a premalignant lesion and be treated as such.

Invasive carcinoma is present in 5% of all adenomas, but the incidence correlates with the size and type of the adenoma (Table 49-8).

<table>
<thead>
<tr>
<th>TABLE 49-8: ADENOMATOUS POLYPS AND VILLOUS ADENOMA: SIZE, HISTOLOGIC TYPE, AND PERCENTAGE OF CARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histologic Type</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Tubular adenoma</td>
</tr>
<tr>
<td>Intermediate type</td>
</tr>
<tr>
<td>Villous adenoma</td>
</tr>
</tbody>
</table>


The Haggitt classification, which defines 4 levels within the polyp, has evolved as a useful tool to describe the degree of cancer invasion into a pedunculated or sessile adenomatous polyp. This classification forms the basis of the management of malignant polyps (Fig. 49-2). In Haggitt levels 1, 2, and 3, the risk of lymph node metastasis in a surgical specimen is less than
1%, whereas a level 4 invasion of the stalk behaves like a sessile T1 lesion and carries a higher risk of 12% to 25% of having lymph node metastases. A similar, but less well-known, classification was developed in 1993 by Kudo and associates, who for prognostic purposes suggested to divide the submucosal invasion of sessile malignant lesions into 3 levels (Sm1, Sm2, and Sm3) (Fig. 49-3).

**FIGURE 49-2** Haggitt classification of tumor invasion in pedunculated or sessile polyp. Pedunculated polyps: level 0—not invasive carcinoma; level 1—invasion to the head of the pedunculated polyp; level 2—invasion to the neck of the pedunculated polyp; level 3—invasion to the stalk of the pedunculated polyp; level 4—invasion to the base of the pedunculated polyp. Sessile polyps: All lesions are level 4. (Reproduced with permission from Haggitt RC, Glotzbach RE, Soffer EE, et al: Prognostic factors in colorectal carcinomas arising in adenomas: Implications for lesions removed by endoscopic polypectomy, *Gastroenterology* 1985;Aug:89(2):328–336.)
Flat and/or depressed adenomas are a subtype of colonic adenoma with a propensity for high-grade dysplasia in 10% to 41% of affected patients regardless of the small size of these lesions.\textsuperscript{150} The entity was first described in Japan, where they seem to occur at a regular frequency. These lesions, which are flat or slightly raised to less than 2 mm and commonly less than 1 cm in size, may be overlooked easily on colonoscopy and turn into a cancer before having reached a size comparable with classic cancers.\textsuperscript{150-153} Recent screening studies, which took advantage of chromoendoscopy techniques, have confirmed that flat adenomas represent up to 25% to 36% of all polyps found in a random cohort and are present in 8% to 11% of the population.\textsuperscript{153,154}

**Hamartomatous Polyps.** A hamartomatous polyp is composed of a spectrum of different cellular elements and is considered a nonneoplastic entity with no significant premalignant potential.\textsuperscript{155,156} Several clinical syndromes manifest with a polyposis of hamartomatous polyps (eg, juvenile polyposis, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Cronkite-Canada syndrome), and these have been discussed earlier in this chapter. These syndromes carry varying risks of intestinal and extraintestinal disease, and several also impose an increased likelihood of developing intestinal cancer due to immature glandular elements in the hamartomatous polyp. Stable estimates of this risk are difficult to calculate because of the relative rarity of these diseases.
**Hyperplastic Polyps.** Hyperplastic polyps are small, sessile mucosal outgrowths that display an exaggerated crypt architecture. They are usually small, with only very few (1%-4%) larger than 1 cm; however, these larger polyps actually may be serrated adenomas rather than hyperplastic polyps (see the following text). Within the colorectum, hyperplastic polyps commonly have a distal distribution pattern, predominantly in the rectum and sigmoid colon, and they have been reported in up to 75% of patients older than 60 years at autopsy. It is not unusual to find several of these polyps in a single individual.

Histologically, hyperplastic polyps display well-formed glands and crypts that are lined by nonneoplastic epithelial cells. Because of their small size, hyperplastic polyps are generally clinically silent, but large or multiple hyperplastic polyps occasionally can be responsible for gastrointestinal symptoms.

Historically, hyperplastic polyps have been considered benign and not premalignant. This paradigm has been increasingly questioned, beginning in 1990 with work by Longacre and Fenoglio-Preiser. The ability of hyperplastic polyps to develop defective mismatch repair genes and foci of microsatellite unstable cancers has been documented, strengthening this concept. Additional research has illuminated an epigenetic pathway, whereby a promoter region in the DNA of hyperplastic polyps is methylated, resulting in progression along a sequence of steps that leads to a serrated adenoma and eventually carcinoma. The clinical significance of hyperplastic polyps and serrated adenomas is a topic of emerging importance in the field of colorectal cancer prevention.

As with adenomatous polyps, individuals who have a predisposition to developing hyperplastic polyps may be at increased risk for developing colorectal cancer. The endoscopic and radiologic appearance of the mucosal abnormalities in hyperplastic polyposis closely resembles FAP, but the syndrome is not believed to be heritable and does not have any extraintestinal manifestations. The World Health Organization (WHO) has defined criteria for this entity as follows: (1) at least 5 histologically diagnosed hyperplastic polyps of which 2 are greater than 20 mm or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in someone who has a first-degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size that are distributed throughout the colon and rectum.
The risk of colorectal cancer being present or developing subsequently in a patient meeting these criteria is high in case series, but population-based studies have not yet been performed. While prophylactic colectomy has been proposed for patients with hyperplastic polyposis, there are no consensus opinions at this time regarding the appropriateness of this approach. At a minimum, a program of intensive colonic surveillance is indicated.

**Inflammatory Polyps.** Inflammatory polyps are the result of reactive regenerative processes occurring in or next to a damaged epithelium. Because of the extent and chronicity of IBD, inflammatory polyps are most commonly seen in that context. The prominence of inflammatory pseudopolyps often is the result of the presence of adjacent ulcerations. Histologically, a combination of distorted crypt architecture in conjunction with granulation tissue and inflammatory infiltrates is characteristic. Even though the underlying chronic IBD represents a high risk for colorectal cancer, the inflammatory polyps as such do not carry a malignant potential. Biopsies in IBD should therefore also include the more flat-appearing areas rather than the polyps only.

**POLYP TRANSFORMATION**

By definition, the neoplastic nature of an adenomatous polyp represents dysplasia. In an effort to quantify the clinical severity/importance of dysplasia, however, the degree of dysplasia is categorized and reported in 3 grades. This categorization is based on the histopathologic differentiation and architecture of the epithelial cells within the polyp.

Common terms for polyps include *low-grade dysplasia*, *intermediate-grade dysplasia*, and *high-grade dysplasia* (by some also referred to as *in situ [Tis] adenocarcinoma*). Once there are clear microscopic features of tumor invasion through the muscularis mucosa of the colorectum, an invasive cancer (T1 or greater) is present. This important demarcation is based on the finding that lymphatic vessels are almost never found superficial to the muscularis mucosa. The descriptive terms for invasive cancer include *well-differentiated* (grade I), *moderately differentiated* (grade II), or *poorly differentiated* (grade III) adenocarcinoma.
MANAGEMENT OF COLORECTAL POLYPS

The overarching goal of physicians treating patients with colorectal polyps is to minimize the risks associated with invasive malignancy, while simultaneously avoiding complications of diagnosis and treatment. Colorectal cancer prevention programs are widely believed to reduce the risk of colorectal cancer mortality through endoscopic removal of premalignant lesions and the detection of invasive lesions at a point in their progression where they are asymptomatic. The efficacy of colorectal cancer prevention programs has been proven in multiple randomized and nonrandomized studies. 144,165-169

The majority of colonic polyps can be removed via colonoscopy, but this may not be the case for 1 of 2 reasons. First, a polyp may not be resectable due to size, attachment to bowel wall, or other reasons related to the anatomy of the patient or polyp. In these situations, a careful assessment of the risks of surgical resection versus observational management is warranted, as 12% to 18% of these polyps harbor an invasive malignancy. 170-172 Second, polypectomy may not be reasonable in the presence of innumerable polyps.

When invasive cancer is found in a polyp, the management is based mainly on the level of invasion and the completeness of the polypectomy. Based on Haggitt’s observations (see Fig. 49-2), it has been suggested that colonic cancers invasive to Haggitt levels 1, 2, and 3 can be adequately treated with polypectomy (2-mm margin), whereas polyps with invasion into Haggitt level 4 should be treated like a sessile lesion. 148,173

Management of sessile lesions is more controversial. If a sessile lesion cannot be snared in 1 intact piece with a microscopically clear margin of at least 2 mm or if it demonstrates lymphovascular invasion or deep invasion into level Sm3 (lower third of submucosa) (see Fig. 49-3), the patient should undergo a formal oncologic resection of the colon. The approach for an adequately removed lesion with a lesser extent of invasion into the submucosa—Sm1 (invasion only into upper third of submucosa) or Sm2 (invasion only into upper two-thirds of submucosa)—should be individualized based on the risk of a surgery versus the risk of lymph node metastases. 173,174 It is advisable in any case to tattoo the area of a suspect polyp endoscopically with India ink for later identification of the site.
Malignant Tumors of the Colon

The vast majority of malignant colon neoplasms are cancers (carcinoma), that is, malignant neoplasms of epithelial origin. Based on the endodermal glandular tissue origin, adenocarcinoma and its histologic variants are by far the predominant histopathology and account for 90% to 95% of all colorectal malignancies. The majority of this section is therefore devoted to these types of tumors, but it also briefly discusses nonepithelial tumors of the colon.

ADENOCARCINOMA

Colorectal cancer (adenocarcinoma) is the most frequent malignancy of the gastrointestinal tract, the fourth most frequently diagnosed malignancy, and the fourth most common cause of cancer-related mortality in the world.\textsuperscript{175} Squamous and adenosquamous carcinomas are exceptionally rare and are located characteristically in the rectoanal junction. The histopathologic classification of colorectal cancer as defined by the WHO is illustrated in Table 49-9.

\textbf{TABLE 49-9: WHO HISTOPATHOLOGIC CLASSIFICATION OF COLORECTAL CANCERS AND THEIR SIGNIFICANCE}
<table>
<thead>
<tr>
<th>Histopathologic Types</th>
<th>Pathology</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>90%-95% of the colorectal malignancies</td>
<td>Controversial whether mucinous histology itself is an independent negative prognostic factor</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>10% of all colorectal cancers; the extracellular type is more common than the intracellular type</td>
<td></td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma (oat cell)</td>
<td>&lt;1%; histologically identical to small cell carcinoma of the lung</td>
<td>Extremely poor prognosis and almost all cases have lymph node, liver, and brain metastasis</td>
</tr>
<tr>
<td>Small cell adenosquamous carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma (medullary)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Macroscopically, most colorectal cancers have either a polypoid or an ulcerative-infiltrating appearance, but combinations are frequent. Very rarely, colorectal cancer may have a dissolute growth pattern and resemble linitis plastica of the stomach, in which case a metastatic lesion from another primary site (eg, lobular breast cancer, stomach cancer) or a nonepithelial neoplasia (eg, lymphoma, carcinoid) would need to be ruled out.

Adenocarcinoma, the exceedingly predominant histopathology of colon...
cancer, has a less frequent variant of mucinous adenocarcinoma that includes signet ring cell carcinoma and accounts for approximately 10% of all colorectal cancers. Compared to nonmucinous colon cancers, mucinous carcinomas usually present at a more advanced stage and thus have an overall poorer prognosis.  

A rare variant of colorectal cancer is small cell cancer, which accounts for less than 1% of all cases and, similar to small cell cancer of the lung, appears to be related to some degree to a neuroendocrine origin. These tumors have a high tendency to develop widespread metastasis early in the course and have an extremely poor prognosis.  

The distribution of colorectal cancers among the various segments has seen a continued shift toward right-sided colon cancer. An estimated 45% to 55% of colorectal cancers are located in the rectum (10%-15%) or sigmoid colon (40%), and 25% to 35% are located in the cecum or ascending colon, whereas the remaining are equally distributed through the rest of the colon. The local growth pattern for colorectal cancer involves circumferential and transmural invasion of the tumor through the intestinal wall into the peritoneal cavity or surrounding organ structures. Tumor dissemination primarily occurs through access to the lymphatic vessels into the locoregional lymph nodes or through access to the bloodstream as hematogenous metastasis to distant organs. The most common site of bloodborne spread is via the portal venous system to the liver; other secondary locations include the lung or, less frequently, kidneys, bone, and other sites. In addition, tumor dissemination can occur by transperitoneal seeding and result in peritoneal carcinomatosis. Following gravity, peritoneal seeds may accumulate in the pelvic cul-de-sac or paracolic gutters where they can grow to a considerable size (Blumer’s shelf). Growth by perineural infiltration may be seen on microscopic examination and has a negative prognostic impact. About 20% of the patients have evidence of distant metastases (stage IV disease) at the time of presentation.

**STAGING OF COLON CANCER**

Modern staging of colorectal cancer defines 4 clinical stages (I-IV) based on the TNM (tumor-node-metastasis) system, which has just recently been updated by the American Joint Committee on Cancer (AJCC) (Tables 49-10 and 49-11). Independent parameters are (1) the depth of tumor
invasion (T) into or through the layers of the intestinal wall with or without invasion of adjacent organs, (2) the number of regional lymph nodes involved (N), and (3) the presence or absence of distant metastases (M). Additional modifiers are used to reflect the method of stage determination (p for pathology, c for clinical, u for ultrasound); y indicates the status after neoadjuvant treatment.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumor (T)</td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
</tbody>
</table>
| Tis | Carcinoma *in situ*, intramucosal carcinoma  
(involvement of lamina propria with no extension through muscularis mucosae) |
| T1 | Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria) |
| T2 | Tumor invades the muscularis propria |
| T3 | Tumor invades through the muscularis propria into pericolorectal tissues |
| T4 | Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure |
| T4a | Tumor invades through the visceral peritoneum  
(including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum) |
| T4b | Tumor directly invades or adheres to adjacent organs or structures |
| Regional lymph nodes (N) | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | One to three regional lymph nodes are positive  
(tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative |
| N1a | One regional lymph node is positive |
| N1b | Two or three regional lymph nodes are positive |
| N1c | No regional lymph nodes are positive, but there are tumor deposits in the  
* subserosa  
* mesentery  
* or nonperitonealized pericolic, or perirectal/ mesorectal tissues. |
| N2 | Four or more regional nodes are positive |
| N2a | Four to six regional lymph nodes are positive |
| N2b | Seven or more regional lymph nodes are positive |
| Distant metastasis (M) | |
| M0 | No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs (This category is not assigned by pathologists.) |
| M1 | Metastasis to one or more distant sites or organs or peritoneal metastasis is identified |
| M1a | Metastasis to one site or organ is identified without peritoneal metastasis |
| M1b | Metastasis to two or more sites or organs is identified without peritoneal metastasis |
| M1c | Metastasis to the peritoneal surface is identified alone or with other site or organ metastases |

Abbreviation: TNM, tumor-node-metastasis.
Historical classifications such as Dukes and Astler-Coller are still sporadically in use but largely have been and should be abandoned. Because the extent of tumor resection (complete vs incomplete) strongly correlates with prognosis, the AJCC released additional guidelines to reflect the extent of residual tumor after a surgical resection with the letter *R* (see Table 49-10).\(^{183}\)

### Nonepithelial Tumors of the Colon

**BENIGN NONEPITHELIAL TUMORS**
Lipomas and Lipomatous Polyposis. Lipomas are submucosal lesions that develop in the fifth or sixth decade of life and are more common in the large than in the small intestine. Histologically, the polyps consist of a submucosal lump of adipose tissue that is covered with a normal colonic mucosa. Whereas solitary lipomas tend to occur more frequently on the right side of the colon in the vicinity of the ileocecal valve or the ascending colon, *lipomatous polyposis* may diffusely involve the entire small and large intestine.

Lipomas generally are asymptomatic but may be found incidentally on colonoscopy. The characteristic appearance is a smooth mass with normal overlying mucosa. The soft nature of the lipoma can be demonstrated by poking the tumor with an endoscopic instrument (“pillow test”). Asymptomatic, incidentally detected lesions should be left alone.

Occasionally, when lipomas become large enough to protrude into the lumen, they may cause symptoms such as gastrointestinal bleeding, diarrhea, intussusception, or bowel obstruction. Endoscopic removal of such a lipoma with a snare often is possible but has a risk of hemorrhage because the fat may prevent the cautery from adequately transmitting the energy to the blood vessels in the stalk. Surgery may be required if such a complication occurs; therefore, it should be considered preemptively for very large symptomatic lipomas. Alternatively, the mucosa overlying the lipoma may be opened endoscopically to allow the lipoma to spontaneously enucleate into the lumen.

Potentially Malignant Nonepithelial Tumors of the Colon

Carcinoid or Neuroendocrine Tumors. Modern nomenclature classifies carcinoids as neuroendocrine tumors based on their neuroendocrine origin. They are characterized by subepithelial nests of epithelial-appearing cell elements. Carcinoid tumors may occur anywhere in the entire body. A recent study on 11,427 patients from the SEER database found that the gastrointestinal tract is affected in 55% of patients, with the most frequent locations being the small intestine (44.7%), the rectum (19.6%), the appendix (16.7%), and the colon (10.6%), a finding that contrasts with traditional reports that the appendix is the most frequent site in the gastrointestinal tract. The annual incidences for the colon and rectum were reported to be 2.0 and
4.2 cases per 100,000 people per year, with the risk of metastasis proportional to the size of the carcinoid. Unlike most neoplasms, invasiveness of carcinoid tumors is not entirely based on histologic criteria (eg, invasion of muscularis propria) but includes clinical aspects. In absence of other definite indicators for malignant behavior, carcinoids smaller than 1 cm are considered benign, lesions larger than 2 cm are likely malignant, and the gray zone in between remains undetermined or potentially malignant. Malignant carcinoids may spread locoregionally into the lymph nodes or directly to the liver.

Patients with a gastrointestinal carcinoid tumor may be either completely asymptomatic or present with intestinal obstruction, bleeding, carcinoid syndrome, or carcinoid heart disease, that is, acquired and commonly right-sided valvular heart disease. Vasoactive substances (eg, serotonin and 5-hydroxyindolacetic acid [5-HIAA]) are released from carcinoid tumors but for the most part are eliminated in a hepatic first-pass effect before reaching the systemic circulation. Carcinoid syndrome is therefore a bad prognostic sign because it does not typically develop until metastatic lesions in the liver directly release their products into the systemic circulation. Hindgut carcinoid tumors (those located in the distal transverse colon and beyond) classically do not cause carcinoid syndrome because they are less endocrinologically active.

Diagnosis of a carcinoid may be suspected clinically but can be difficult to confirm histologically short of a surgical resection because the lesions are submucosal and not commonly in reach of an endoscopic biopsy. A preoperative workup for a carcinoid tumor should include a 24-hour urine collection of 5-HIAA and a plasma chromogranin A. Both parameters can also be used for postoperative surveillance. Cross-sectional imaging and somatostatin receptor scintigraphy are tools to evaluate for systemic disease. Multicentricity and associated high rates of synchronous gastrointestinal and genitourinary malignancies warrant both an upper and lower gastrointestinal endoscopy.

An oncologic resection should be performed in all carcinoids larger than 2 cm unless contraindicated by clinical circumstances. Tumors less than 1 cm in size may be managed locally, whereas the management of lesions measuring 1 to 2 cm remains controversial.

**Gastrointestinal Stromal Tumors (GISTs).** GISTs are the most common mesenchymal tumors of the gastrointestinal tracts and originate from the
intestinal pacemaker cells, the interstitial cells of Cajal. Sixty percent of GISTs are found in the stomach; 29% in the small intestine; 2% in the colon, rectum, and rectovaginal septum; and 9% in the esophagus. Symptoms are nonspecific and include pain, obstruction, bleeding, and a mass. Distinction from other mesenchymal tumors (eg, leiomyosarcoma) is important from a prognostic point of view. Tumor size and light microscopic determination of the mitotic rate (mitotic figures per x number of high-power fields) are the most important conventional prognostic indicators. The diagnosis of GISTs is based on morphologic features and immunohistochemical demonstration of c-kit (CD117) expression. This marker is seen in almost all GISTs and is regarded as one of the key diagnostic elements, but a few otherwise characteristic tumors are found to be c-kit negative. While the majority of GISTs have activating mutations of the KIT receptor tyrosine kinase, another subset of tumors show mutations in the KIT-related kinase gene platelet-derived growth factor receptor alpha (PDGFRA). KIT and PDGFRA mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs. Determination of CD117 expression is of practical importance because positivity correlates with a tumor response to treatment with imatinib (Gleevec), which inhibits KIT kinase activity. Surgical resection is the primary treatment for localized GISTs that are resectable without mutilation. Recurrent and locally advanced or metastatic tumors are treated increasingly with imatinib in a palliative, adjuvant, or neoadjuvant setting.

**Nodular Lymphoid Hyperplasia.** This condition is characterized by numerous polyps in the small and large intestine, rarely in the stomach, which consist of enlarged submucosal lymphoid follicles. Associated diseases are immune deficiencies of various origins (eg, tumors, hematoproliferative disorders, immunoglobulin A deficiency, and human immunodeficiency virus [HIV] infection), in which case recurrent infections (eg, giardiasis) appear to promote the nodular lymphoid hyperplasia. Immunocompetent patients usually are asymptomatic, and the nodular lymphoid hyperplasia is an incidental finding. Nodular lymphoid hyperplasia has been associated with an increased subsequent incidence of lymphoma (small bowel).
Lymphoma. Primary malignant lymphoma of the colon is uncommon and accounts for only 0.2% to 0.4% of all colonic malignancies and 10% to 15% of all primary lymphomas of the gastrointestinal tract, which themselves account for about 30% of extranodal lymphomas.\textsuperscript{196} The most frequent colonic location is the cecum (70%), followed by the rectum and ascending colon. The gross appearance may be a circumferential or polypoid mass, an ulceration, or a diffuse infiltration with stricturing and bowel wall thickening.\textsuperscript{197} Eighty-six percent of the lesions are solitary, but they can be multiple and diffuse in nature. The intestinal lymphomas may be subclassified into B-cell lymphomas (85%) and T-cell lymphomas (15%). Among the B-cell lymphomas, mantle cell lymphoma has a worse prognosis, whereas mucosa-associated lymphoid tissue (MALT) lymphomas have a better prognosis than other B-cell tumor types.\textsuperscript{197} While surgical treatment may be indicated for some localized tumors, many authors consider medical management to be the primary treatment. It may include new approaches such as anti-infectious treatment for MALT lymphoma or reconstitution of the patient’s immune status, for example, by means of antiretroviral treatment in HIV-associated B-cell lymphoma.\textsuperscript{198}

Multiple lymphomatous polyposis of the gastrointestinal tract is a distinct clinicopathologic entity. This rare form of primary gastrointestinal lymphoma occurs most often in elderly patients and accounts for 9% of all gastrointestinal lymphomas.\textsuperscript{199} The polyps can be widespread throughout multiple segments of the gastrointestinal tract. Histopathologic and immunohistochemical techniques are required to differentiate lymphomatous polyposis from other forms of gastrointestinal polyposis.

Kaposi Sarcoma. This commonly multifocal angiosarcoma has been associated with herpesvirus-8 (HHV-8) infection in conjunction with immunosuppression (eg, HIV/AIDS, chronic steroid or immunosuppressant medication). The incidence in organ transplant recipients is about 0.5% to 0.6% but most frequently involves the skin. In rare cases, however, the anorectum or intestines are involved and show characteristic bluish-purple submucosal nodules. Treatment is primarily aimed at improving the immune status, but chemotherapy and, rarely, radiotherapy may be indicated in patients in whom the immune status cannot be restored.\textsuperscript{200}
Smooth Muscle Tumors. Smooth muscle tumors of the colon are rare and occur most commonly in the form of a pedunculated leiomyoma of the muscularis mucosa. Leiomyosarcomas, which consist histologically of spindle cells that resemble smooth muscle cells, are even less frequent but are characterized by an extremely aggressive and rapidly fatal growth pattern. Whenever possible, oncologic resection and adjuvant chemotherapy are the treatment of choice.²⁰¹

SECONDARY TUMORS TO THE COLON

Endometriosis. Endometriosis may involve the colon or rectum in approximately 15% to 20% of cases and may mimic colonic carcinoma. The lesions are rarely larger than 5 cm, involve the subserosa and muscle coats, and may project into the lumen of the bowel. When endometrial tissue extends through to the colonic mucosa, biopsy may be mistaken for adenocarcinoma.

Invasion From Extracolonic Cancers. Locally advanced tumors from noncolonic primary cancers may directly invade the colon and cause symptoms suggestive of colon cancer (bleeding, obstruction, fistula). These tumors originate from organs in close adjacency to the colon (female organs, bladder, prostate, kidneys, pancreas, duodenum, liver).

Metastatic Cancer. Carcinomas from other primary sites may metastasize to the colon and occasionally mimic a primary colon cancer. Metastases originate most commonly from lobular breast cancer, stomach cancer, ovarian cancer, malignant melanoma, and leukemia, the latter of which can be diagnosed by the hematopoietic infiltrates.

SURGICAL ANATOMY OF THE COLON

A fundamental knowledge of the anatomy is unquestionably a key to success-oriented surgical technique aimed at the best oncologic outcome and a minimized morbidity. The large intestine starts at the ileocecal junction and extends to the anus. It is about 5 to 6 ft (125-150 cm) long and can be divided into the cecum with the appendix, the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum. Definitions of
where the sigmoid colon ends and the rectum begins have not always been uniform. The best definition of the rectosigmoid junction from a functional and surgical viewpoint is the confluence of the teniae coli. However, the inability to visualize this anatomic reference point endoscopically recently led the NCI and other expert committees to define the rectum for the purpose of uniformity in clinical trials as the last 12 to 15 cm above the anal verge as measured by rigid sigmoidoscopy. This endoscopic definition is necessary in order to determine the appropriateness of preoperative (neoadjuvant) chemoradiation for rectal but not sigmoid cancer. Obsolete, variable, and thus inaccurate definitions relate the rectosigmoid junction to the level of (1) the peritoneal reflection or (2) the sacral promontory.

The arterial and venous blood supply and the lymphatics of the colon are summarized in Figure 49-4. The arterial blood supply to the colon comes from the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA), which communicate in a watershed area in the splenic flexure (artery of Drummond). The rectum has additional branches from the internal iliac vessels. With a significant degree of anatomic variation, the major vascular stalks to the colonic segments consist of the ileocecal and right colic artery (last branch of the SMA), the middle colic artery (second branch of the SMA), the left colic artery (first branch of the IMA), and the superior hemorrhoidal artery (distal branch of the IMA). The venous blood supply peripherally follows the arterial branches but more centrally divides into the superior mesenteric vein and the inferior mesenteric vein, which connect at separate levels to the portal system. The lymphatic drainage starts with lymphatic follicles in the colonic submucosa, drains through the colonic muscle wall into the epicolic nodes, and continues to the paracolic lymph nodes that follow the blood vessels to the bowel, along the major arteries to the principal lymph nodes at the level of the arterial runoff from the aorta. These lymph node groups consist of the celiac, the superior mesenteric, and the inferior mesenteric groups of lymph nodes.
For a safe surgical technique, the relationship of the colon with adjacent structures, mostly in the retroperitoneum, has to be fully understood. The colon is only a partially intraperitoneal organ. Only the transverse colon and the sigmoid colon are fully peritonealized and have a free mesocolon; the ascending colon and the descending colon, including both flexures, are partially located in the retroperitoneum and therefore reside in proximity to essential anatomic structures. The structures most at risk during a right hemicolectomy include the right ureter and the duodenum; during a transverse colon resection, the SMA/superior mesenteric vein (and its branches) and the gastroepiploic vessels at the gastric curvature; during a takedown of the splenic flexure, the spleen, pancreas, and left kidney; and during a left colon or sigmoid resection, the left ureter, the gonadal vessels, and the hypogastric nerves.

**CLINICAL PRESENTATION OF COLORECTAL CANCER**

**Symptoms and Differential Diagnosis**
Colorectal cancer does not have any early signs. In fact, symptoms are often absent until a tumor has grown to a significant size. Unless a patient presents with a tumor complication (eg, bowel obstruction, bleeding, perforation, or fistula formation), symptoms mostly are subtle or uncharacteristic and vague. They may consist of unexplained weight loss, anemia and weakness from chronic blood loss, flatulence, or episodes of colicky abdominal pain. If present, these symptoms therefore always should be suspicious for a locally relatively advanced tumor stage, which is also reflected by the fact that about 20% of colorectal cancer patients at the time of their first presentation already have stage IV disease with distant metastases (Table 49-12). Because the stool in the proximal colon is still liquid or at most semisolid, proximal colon tumors may grow to relatively large size before they cause an obstruction. The more distal a lesion is localized (eg, left colon or rectum), the more likely the changes in bowel habits occur. These include rectal bleeding or mucous discharge in or with the stool, sudden onset of constipation, alternating periods of diarrhea and constipation, or a decreasing diameter of the stool. Pelvic or anal pain is an ominous sign because it may occur with increasing size, perforation, or sphincter invasion of a rectal cancer.

**TABLE 49-12: DISTRIBUTION OF SINGLE COLON PRIMARY CANCER BY STAGE**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, I</td>
<td>1845</td>
<td>37.8</td>
</tr>
<tr>
<td>II</td>
<td>1085</td>
<td>22.2</td>
</tr>
<tr>
<td>III</td>
<td>825</td>
<td>16.9</td>
</tr>
<tr>
<td>IV</td>
<td>955</td>
<td>19.6</td>
</tr>
<tr>
<td>Unspecified</td>
<td>168</td>
<td>3.4</td>
</tr>
</tbody>
</table>


Any large bowel obstruction, bleeding per rectum, gas or stool passage other than through the anus, or peritoneal signs should raise the index of suspicion for a colorectal malignancy until proven otherwise. Several other conditions and diseases have to be considered in the differential diagnosis. Obstructive symptoms may result from chronic diverticulitis, benign polyps,
Crohn’s disease, endometriosis, or a postischemic stricture. A fistula may suggest complicated diverticulitis, Crohn’s disease, or tuberculosis. Bleeding per rectum may also be found in hemorrhoids and other benign anorectal conditions, diverticular disease, arteriovenous malformations, endometriosis, and proctitis or colitis. However, even if 1 of these benign diseases is found on clinical evaluation, the symptoms should not be attributed automatically to them before a malignant disease of the large intestine has been ruled out.

Because symptoms are not reliable for the prevention or early detection of colorectal cancer, risk-adjusted screening programs for otherwise asymptomatic individuals (as discussed in an earlier section of the chapter) are crucial in order to achieve a reduction in cancer mortality.

Management planning in a situation with acute cancer complications should include strategies to alleviate symptoms and minimize the morbidity from the complication and also provide an oncologically adequate treatment for the tumor.

**History and Physical Examination**

A careful history and physical examination remain the cornerstone in all patients presenting with gastrointestinal symptoms. This review should include questions about changes in bowel habits, time of last stool and gas passage, weight loss, and a personal or family history of cancer, particularly of colorectal cancer or its precursor lesions. Awareness of possible underlying diseases and genetics that predispose to colorectal cancer is of utmost importance not only for the management of the individual patient, but also for adequate counseling of potentially affected family members.

A careful physical examination follows to identify any palpable tumor masses and/or signs of tumor complication or dissemination. Apart from vital signs and temperature, the patient’s general appearance may reveal evidence of cachexia, dehydration, jaundice, or lymph node enlargements. For example, enlargement of the left supraclavicular nodes may be the first but late sign of a disseminated gastrointestinal malignancy (Troisier sign). The abdomen is examined for a palpable primary tumor, hepatomegaly (liver metastasis?), distension, and/or tympanitic bowel sounds (partial or complete bowel obstruction?). Presence of peritoneal signs such as guarding with local direct and rebound tenderness or percussion tenderness may indicate a tumor perforation. A digital rectal examination and proctoscopy are mandatory to
rule out involvement of the rectum or to determine the exact distance of a
distal and possibly palpable tumor from the anal verge, its axial and
circumferential extent, and the mobility of the tumor against surrounding
structures (eg, sacrum, prostate/vagina, anal sphincter muscle). In addition,
the checking finger should assess the rectal vault for the presence of stool,
blood, or melena.

A thorough general physical examination is necessary to evaluate the
patient’s general health status regarding the ability to tolerate a major
abdominal procedure under general anesthesia. Particular attention has to be
paid to patients who present with acute symptoms in an emergency setting.
Prolonged fasting, nausea or vomiting, and translocation of fluids into the
third space during a period of bowel obstruction or after a perforation will
rapidly result in a state of malnutrition and dehydration. Developing sepsis or
acute and recurrent blood loss potentially aggravate these symptoms and may
result in a severe volume loss. Alarming signs are a decrease in urine output,
tachycardia, hypotension, elevated temperature, short-term weight loss,
standing skin folds, dry oral mucosa, and acidosis. Immediate fluid and
volume resuscitation has to parallel the further clinical workup and
monitoring. Blood tests have to be interpreted with caution; for example,
dehydration may result in an artificially high hematocrit and mask a
significant loss of blood.

**Investigations**

Patients with symptoms suggestive of colorectal cancer should undergo a
series of timely investigations with 3 goals: (1) to assess the large bowel
regarding the primary lesion, concomitant lesions, and a potential underlying
colonic disease; (2) to determine whether the tumor has metastasized; and (3)
to assess the patient’s operability (overall condition and comorbidities).

**COMPLETE EVALUATION OF THE LARGE INTESTINE**

Irrespective of the method used, the primary goal is to document the presence
of a malignant pathology and to rule out concomitant lesions in other
segments of the large intestine. Both endoscopic and radiologic techniques
are available for evaluation of the colon and rectum, and each type of
examination has inherent strengths and weaknesses.
**Rigid Proctoscopy and Flexible Sigmoidoscopy.** These first-line diagnostic tools are used mostly in the outpatient setting to accurately assess lesions in the distal colon and rectum. The 2 methods are rapid, widely available, and require only minimal bowel preparation (enema). However, they do not provide complete information about the rest of the colon, and therefore, a complementary study is indicated before surgery. Furthermore, the flexible sigmoidoscope is notorious for giving inaccurate measurements of the level of the tumor. Determination of the rectal versus colonic location of the tumor should be done with a rigid proctoscope.

**Colonoscopy.** Conventional white light colonoscopy is currently the gold standard for the detection and treatment of colorectal polyps. It provides accurate information about the entire colonic mucosa (ie, polyps, synchronous cancer, colitis, melanosis, and diverticula), and it may be used to remove synchronous neoplastic polyps. Apart from determining the circumferential and longitudinal extent of a colonic lesion, colonoscopy addresses functional aspects such as active bleeding or an imminent obstruction by cauterization, laser ablation, or placement of a self-expanding metallic wall stent, hence allowing for turning an emergency situation into an elective one.

While the overall risk of colonoscopy is very low with a much less than 1% incidence of bowel perforation, there are some limitations to the technique. There is an estimated 10% incidence that the cecum may not be reached as a result of technical reasons. In addition, the precise position of a lesion seen on colonoscopy may not be determined adequately unless 1 of the 2 absolute landmarks (dentate line or the carpet-like villi of the terminal ileum) is in direct proximity. Relative landmarks (eg, assessment of the endoscopic shape of the colon, liver and spleen shadow, ileocecal valve, appendiceal orifice) and the length of instrument insertion from the anal verge vary considerably and should not be used. In practical terms, however, this handicap may be overcome by India ink tattooing of the area of a lesion for better identification during surgery or repeat endoscopy.

Studies have shown that 22% of polyps may be missed on the initial colonoscopy. Furthermore, flat and depressed lesions are difficult to visualize during conventional colonoscopy using white light. New advances in endoscopy visualization help increase the detection rate of lesions that would otherwise be missed.
Chromoendoscopy involves the use of dyes or compounds (eg, methylene blue and indigo carmine) that highlight differences on mucosal surfaces, which increases the detection of neoplastic polyps compared with conventional colonoscopy.\textsuperscript{206} Once a lesion has been identified, the dye also allows the demarcation of the affected area to ensure complete removal during polypectomy. To answer the question about whether the use of dye spray increases the detection of polyps and neoplasia during colonoscopy, there have been a number of randomized controlled trials comparing chromoendoscopy with conventional colonoscopy. A recent Cochrane review analyzed 5 such trials and found a significant difference in favor of chromoendoscopy for all detection outcomes.\textsuperscript{207}

Because the application of dye spray on colonic mucosa during chromoendoscopic examination may be cumbersome and time consuming, there have been technologic developments that have been able to improve the contrast between normal and neoplastic mucosa without using dyes. Narrow-band imaging (NBI) is one such modality, where the use of bandwidth filters increases the blue spectrum intensity of the light used. This lower wavelength is more readily absorbed by hemoglobin and is less able to penetrate surfaces, thereby enhancing the visualization of superficial capillaries. Because tumors are angiogenic, the vascular network is more prominent and has a higher density in neoplastic tissue than normal mucosa.\textsuperscript{208} The advantages of NBI include enhancing contrast at the push of a button on the colonoscope and the ease of differentiating between neoplastic and nonneoplastic lesions. However, NBI results in poorer illumination of the background. Studies that have compared NBI versus chromoendoscopy demonstrate equivalent adenoma detection rates and similar abilities in differentiating between neoplastic and nonneoplastic lesions.\textsuperscript{209,210}

Other new developments include FICE (Fujinon intelligent color enhancement),\textsuperscript{211} autofluorescence imaging,\textsuperscript{212,213} and i-Scan,\textsuperscript{214} which improve tissue contrast by optical means. Zoom endoscopy using magnification may be combined with different modalities to help further characterize colonic lesions.\textsuperscript{215,216} Confocal laser endomicroscopy combines the benefits of confocal microscopy with endoscopy and provides live in vivo high-resolution optical sections of tissue. It may be particularly useful in the surveillance of patients with long-standing ulcerative colitis, reducing the number of random biopsies.\textsuperscript{217,218}
Contrast Enema. Radiographic contrast enemas alternatively can be used for a colonic evaluation. Contrast enemas are an especially valuable adjunct to colonoscopy in patients with near-obstructing colonic lesions. Furthermore, they have the advantage of more accurately visualizing the anatomic position of a colonic lesion (road map). Ideally, a barium-air double-contrast technique will be used after bowel cleansing; however, in a more acute setting, particularly if there is suspicion of a colonic perforation, administration of barium is contraindicated (risk of barium peritonitis), and instead, a water-soluble contrast material (eg, Gastrografin [diatrizoate meglumine]) should be used in a single-column technique.

The typical aspect of a colon cancer is a fixed filling defect with destruction of the mucosal pattern in an annular configuration (“apple core”), as opposed to an intact mucosal pattern in a filling defect from an extramucosal compression or from chronic diverticulitis. Although preoperative histologic confirmation of a colon cancer is preferable, an unequivocal and characteristic morphology on a barium enema or endoscopy is sufficient evidence to proceed to surgery. The advantages of contrast studies include better passage through even severely obstructing lesions and the fact that they commonly reach the cecum. In addition, they are superior in visualizing diverticula or a suspected fistula between the colorectum and other pelvic organs. The major disadvantage of contrast studies is the inability to take biopsies and to detect small lesions.

Evolving Techniques. CT colonography (“virtual colonoscopy”) and the microcapsule study have evolved in the last decade as high-tech alternatives to the 2 previously described methods. It should be noted that CT colonography still requires patients to undergo a bowel preparation and that air insufflation is necessary. While there is certainly a lot of promise for both new approaches, which likely will continue to improve over time, the definite role of these techniques awaits further clarification.

Early studies suggested that CT colonography had a considerable rate of false-negative and false-positive results. In a recent study of 937 patients with risk factors for colorectal cancer, CT colonography had a sensitivity of 85% for lesions 6 mm or larger. So far, the technology has not been approved by Medicare for screening purposes, but this may change in the future with additional validation studies. Unfortunately, incidental extracolonic findings may precipitate a large number of unwarranted tests,
which add tremendous cost to the health care system. Currently, CT colonography may serve a useful purpose in patients for whom a colonoscopy is undesirable or unsuccessful.

EVALUATION OF THE LOCAL TUMOR EXTENT AND OF METASTATIC DISSEMINATION

Traditionally, the preoperative staging for colon cancer did not mandate further imaging studies because, in the majority of cases, they do not change the local surgical approach. Increasingly, however, preoperative cross-sectional imaging (CT or magnetic resonance imaging) has become the standard of care.\textsuperscript{222,223} The justification for this shift is two-fold. First, patients with a significant burden of liver disease (>50% liver replacement) may carry a prohibitive risk for general anesthesia and should be treated with chemotherapy either in advance of surgery or instead of it. CT scans are the most commonly used cross-sectional imaging technique in the United States and have a 90% and 95% sensitivity and specificity in detecting liver lesions larger than 1 cm.\textsuperscript{224} Second, the surgeon can be alerted to evidence of advanced locoregional disease that may alter the operative plan and necessitate the involvement of other operative expertise (eg, hepatobiliary surgery, urology, gynecology).

To rule out extrahepatic metastases, in particular pulmonary metastases, a chest x-ray in 2 planes commonly is sufficient, although the yield of this test is relatively low. A CT scan of the chest may be necessary to substantiate a concern from conventional images and is only a minimal incremental burden for a patient who is already undergoing such a study of the abdomen and pelvis.

Positron emission tomography (PET) has an evolving role in the evaluation of metastatic disease. While the routine use of PET scanning in the primary management of colorectal cancer is not recommended at this time, this technology does appear to have greater sensitivity for metastatic disease.\textsuperscript{225} The extent to which this greater sensitivity can be translated into an algorithmic approach to staging remains to be seen. Its greatest utility at the current time is (1) in patients in whom systemic disease is suspected (eg, high tumor markers) but not proven and (2) under special circumstances where the presence of previously unknown tumor manifestations (eg, recurrence vs scar tissue, solitary vs multiple liver metastases, and presence
of extrahepatic metastases) would have an impact on the treatment approach (eg, operative vs nonoperative).

LABORATORY AND PREOPERATIVE TESTS

Preoperative laboratory tests are aimed at providing evidence for pathophysiologic effects of the tumor and ruling out general health problems that could have an effect on the patient’s general operability. A comprehensive workup includes a complete blood count, electrolytes, creatinine/blood urea nitrogen (BUN), glucose, liver function tests (alkaline phosphatase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, total protein, albumin), and coagulation parameters (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR]). Arterial blood gas analysis and additional tests will be ordered in an emergency setting or according to the individual patient’s risk assessment (eg, cardiac enzymes).

Even though tumor markers such as carcinoembryonic antigen (CEA) are determined routinely, their role is limited because of the low sensitivity and specificity for colonic carcinoma and because the measured value virtually never changes the management. CEA can also be elevated in proximal gastrointestinal cancers, benign inflammatory conditions of the bowel, lung and breast cancer, and smoking. Nonetheless, CEA level determination may prove helpful in some settings, for example, when the return of an elevated preoperative CEA level to normal indicates a complete tumor resection or when a postoperatively elevated level may indicate residual or recurrent disease.226

Preoperative standard evaluation includes a chest x-ray in 2 planes for cardiopulmonary assessment and for detection of pulmonary metastases (see previous sections). Electrocardiogram (ECG) and pulmonary function tests (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV₁], residual volume [RV], and diffusion capacity) are indicated in patients either older than 40 years or with a respective personal history. Specialized tests such as cardiac stress tests, echocardiogram, perfusion scintigraphy, or interventional cardiologic studies depend on the individual patient’s history and risk assessment.
TREATMENT

Principles of Surgical Management

As a basic principle, any colorectal cancer is an indication for surgery unless widespread tumor dissemination or general contraindications from the patient’s overall health status are present. Furthermore, any precursor pathology with statistical risk for cancer (eg, large sessile polyp in an otherwise healthy individual or dysplasia in a patient with ulcerative colitis) that cannot be managed nonoperatively is an indication for surgery.

The general goal for surgical management is either to achieve cure from the tumor and extension of survival or at least disease-free survival or, in the case of a precursor pathology with or without an underlying disease (eg, ulcerative colitis or FAP), to prevent the cancer and ideally to remove the risk-bearing disease. In a palliative setting, the goal is to prolong the period of symptom-free survival.

Local tumor control generally is the primary treatment objective to prevent local tumor complications, that is, obstruction, perforation, fistula formation, bleeding, and pain. Even in the presence of distant metastases in the liver or lung, resection of the primary tumor remains a reasonable priority. Because solitary or a limited number of metastases in the liver or lung often may be treated surgically by partial organ resection or metastasectomy with a cure rate of up to 35%, their presence should not necessarily alter the surgical approach to do a curative resection at the primary site. However, if there are extensive metastases or peritoneal carcinomatosis and cancer cure is not a reasonable goal, alleviation of symptoms and prevention of impending local complications, for example by restoring the intestinal continuity, are the best palliation.

The specific surgical and oncologic strategy planning is based on a number of factors. It has to take into account the exact localization of the tumor, the tumor stage, the presence of synchronous colonic lesions or an underlying colonic disease, the risk for metachronous lesions, the patient’s age and general condition, the extent of the local procedure, and the timing. Only after the extent of the operation has been defined can the method and approach to be used be discussed as to whether the procedure is only suitable for an open laparotomy approach or laparoscopy may be reasonable and
beneficial.

In contrast to rectal cancer, neoadjuvant treatment (ie, preoperative chemoradiation) is not indicated in the overwhelming majority of colonic cases. In patients with resectable metastases, preoperative chemotherapy followed by a combined colon and liver resection may be an attractive alternative to a staged resection and may help in assessing the tumor response to a particular chemotherapy regimen. Only rarely is a locally very advanced lesion treated with chemotherapy in anticipation of an otherwise unresectable mass. Adjuvant (ie, postoperative) treatment is discussed in a later section.

**PREPARATION FOR SURGERY**

When a patient is considered an operative candidate, several preparatory steps need to be addressed.

**Transfusion.** Most colonic operations can be performed without a blood transfusion. Blood-sparing surgical techniques have reduced the need, while the threshold to transfuse has substantially increased. The indication will depend on the starting hemoglobin, the patient’s age and physiologic status, a history of ischemic events (eg, coronary, stroke), and the extent of expected and real intraoperative blood loss. As a routine, it is recommended to have the patient’s blood typed and screened but to reserve crossmatching units of blood for these higher risk situations.

While the risk of bloodborne infections is very low, there is some controversy as to the immunologic effect of blood transfusions on the overall prognosis of colorectal cancer. Despite an initial report that transfusion may be associated with an increased likelihood of recurrence, many subsequent reports have reached conflicting conclusions. Meta-analysis studies have strongly questioned whether there is a true causal effect present. Other factors such as extent of resection required, tumor location, and experience of the surgeon actually may be the more relevant cause for recurrence, but transfusion may be an indirect reflection of extensive disease and surgery. Furthermore, a randomized trial comparing the use of autologous versus allogenic blood in patients undergoing colorectal resections did not show any statistical difference in prognosis.

**Bowel Cleansing.** Traditionally, bowel cleansing was considered an essential
preparation to any elective colon surgery. The rational is based on the colon being a large reservoir for numerous anaerobic and aerobic bacteria. However, recent prospective, randomized, controlled studies and meta-analyses comparing mechanical preparation versus no preparation for elective colorectal surgery have failed to demonstrate any appreciable decrease in infection rates, anastomotic leaks, or mortality rates in patients undergoing mechanical bowel preparation.\textsuperscript{230-236} Contrasting with the evidence, however, the majority of colorectal surgeons still perform bowel cleansing in their patients. The indisputable advantages of a bowel preparation remain (1) the intraoperative ability to perform a colonoscopy if that were needed and (2) the absence of a preanastomotic stool load if a primary anastomosis or the tissue quality were unexpectedly less than optimal and required a fecal diversion.

There are a wide variety of laxatives, washouts, and enemas available on the market for mechanical cleansing, but the products used generally are based on either polyethylene glycol (eg, GoLYTELY) or sodium phosphate (Fleet Phospho Soda), the latter of which is contraindicated in patients with renal failure and has come under more broad scrutiny in the United States. In the absence of a consensus regarding the best regimens (ie, orthograde cleansing alone or combined with retrograde enemas), the choice often is a matter of personal preference. Depending on an individual patient’s constitution and the degree of obstruction, the bowel cleansing should be started 1 or even 2 days before surgery. The cathartic may result in significant fluid and electrolyte imbalances. Therefore, elderly patients, who are more prone to this adverse effect, should preemptively be given intravenous fluids and electrolytes.

**Antibiotic Prophylaxis.** Perioperative administration of prophylactic antibiotics aims at reducing colonic and dermal bacterial concentrations and is considered a crucial component of colorectal procedures. The benchmark is the rate of surgical site infections in relation to the level of wound contamination. Prophylaxis has to be distinguished from therapeutic antibiotic treatment in patients who already have an established infection. Prophylaxis (ie, in patients who do not primarily suffer from an infection) should be targeted, adequately dosed, and short (ie, start within 1 hour of the incision and be limited to less than 24 hours) in order to minimize antibiotic side effects and propagation of resistances. Coverage should include both
aerobic bacteria (eg, *Staphylococcus, Escherichia coli, Klebsiella, Proteus*) and anaerobic bacteria (eg, *Bacteroides fragilis, Clostridium*).

Intravenous administration of broad-spectrum antibiotics is the most common form of prophylaxis and includes several acceptable antibiotic selections: (1) single antibiotics (ertapenem, piperacillin-tazobactam); (2) combination of 2 antibiotics (second- or third-generation cephalosporin + metronidazole, fluoroquinolone + metronidazole, clindamycin + aminoglycoside, clindamycin + quinolone, clindamycin + aztreonam); or (3) triple combinations, such as amoxicillin-clavulanic acid + metronidazole + aminoglycoside. Oral antibiotics (eg, metronidazole combined with nonabsorbable neomycin) in conjunction with a mechanical bowel preparation may yield similar results but may increase the risk of nosocomial superinfections, in particular with *Clostridium difficile*.

Special considerations according to national guidelines have to be followed for prophylaxis in patients at risk for endocarditis (eg, patients with mechanical heart valve).

**Thromboembolic Prophylaxis.** Thromboembolic prophylaxis is recommended in all patients undergoing major surgical procedures to reduce the incidence of postoperative deep venous thrombosis and pulmonary embolism. Both pharmacologic prophylaxis and physical prophylaxis (eg, pneumatic calf compression) have been proven to be effective, but the use of pharmacologic prophylaxis has been endorsed by a task force recommendation. Both low-dose unfractionated heparin and low-molecular-weight heparins (LMWHs) have been shown to be equally effective in reducing the incidence of postoperative thromboembolic events without resulting in significant complications. A more recent randomized study, however, showed that LMWHs have a slightly higher rate of minor bleeding events. Based on economic analysis, the data favor the use of subcutaneous heparin as being more cost-effective than LMWHs. It is recommended that these drugs be commenced at least 2 hours before surgery and continued postoperatively until the patient has obtained full ambulation. Intermittent pneumatic calf-compression boots are an alternative to heparin that has been demonstrated to be equally successful in preventing deep venous thrombosis and possessing the advantage of no risk of increased bleeding. It remains to be determined whether a combination of chemical agents and pneumatic calf-compression boots for patients undergoing colonic
resection will be an advantage.

Anticoagulated patients who need to take warfarin (eg, due to a mechanical heart valve) should be switched perioperatively to intravenous heparin to allow for stopping the warfarin medication and antagonizing its effect with vitamin K. Four hours before incision, the heparin may be discontinued and resumed within 24 hours postoperatively with a stepwise increase in the dose.

**Urinary Catheters/Stents.** After induction of general anesthesia, bladder catheterization should be performed in all major cases to adequately monitor the urine output peri- and postoperatively. In selected patients with a previous history of colorectal or pelvic dissections, placement of ureteral stents allows better intraoperative identification and protection of these crucial structures. Laparoscopic colon procedures do not routinely need ureteral stents; however, selective use of lighted ureteral stents during challenging laparoscopic procedures may facilitate identification of these structures.

**Nasogastric Tube.** Placement of a nasogastric tube is not necessary on a routine basis for patients undergoing resection of the colon or rectum and should be avoided unless they present with a complete or partial bowel obstruction.²⁴³

**Preoperative Marking of Ostomy Site.** In patients who may need permanent or temporary placement of an ostomy during the surgical procedure, preoperative marking of the ideal stoma site by a stoma nurse helps to facilitate postoperative ostomy handling by the patient.

**Preemptive Pain Management.** Effective pain management is an important factor not just for patient comfort but to reduce the incidence of postoperative pulmonary complications. Preoperative placement of epidural analgesia is a very valuable strategy, which, in addition to its pain-relieving effect, promotes the earlier resumption of postoperative bowel function as a result of its suppression of sympathetic nerves. The relevant segments that need to be blocked for an abdominal incision are located at a thoracic level (T6-T12).

*Surgery*
GENERAL TECHNICAL PRINCIPLES

The objective of surgery for colonic cancer is to perform a curative resection by removing the cancerous segment of colon, the mesentery with the primary feeding vessel and the lymphatics, and any organ with direct tumor involvement. Because the lymphatics run with the arterial supply of the colon, the primary artery supplying the segment of the colon to be resected is divided at its origin. Ligation at the origin of the vessel ensures inclusion of apical nodes, which may convey prognostic significance for the patient. While careful dissection in the right place is the mainstay of a successful surgery, the historical Turnbull no-touch technique with early vascular ligation and occlusion of the bowel with tapes to prevent embolization of tumor and improve survival has not shown any advantage.

The length of bowel and mesentery resected is dictated by tumor location and distribution of the primary artery (Table 49-13), but a radical resection of a colonic tumor should achieve at least a 5-cm clearance at the proximal and distal margin. Extended resections for confined tumors outside of high-risk patients have not been shown to confer additional survival benefit; however, tumors located in “border zones” should be resected with both neighboring lymphatics to encompass possible bidirectional spread. If a tumor is adherent to or invading an adjacent organ such as the kidney or small bowel, an en bloc resection should be performed where technically feasible. Because adhesions between the tumor and adjacent organ may not necessarily be inflammatory but a result of carcinoma, mere division or “pinching” of a tumor from an adjacent organ is not an acceptable surgical technique because it may reduce the chance of cure.

TABLE 49-13: STANDARD RESECTIONS OF THE COLON
When synchronous cancers are present in the colon, an extended resection or even total colectomy, with ideally only 1 anastomosis, should be performed. Occasionally, 2 separate resections (eg, right hemicolectomy and low anterior resection) with 2 anastomoses are preferable to preserve colon length and to avoid postcolectomy diarrhea. Cancer on the basis of an underlying pancolonic disease (eg, ulcerative colitis or FAP) requires a total proctocolectomy with either an ileoanal pull-through procedure or an ileostomy; young patients (<50 years, with or without proven HNPCC gene constellation) presenting with tumors proximal to the sigmoid colon should be offered a total abdominal colectomy to reduce the risk of metachronous cancers and to facilitate surveillance.

A limited wedge resection may be considered for an unfit patient or for palliative resection in those with widespread tumor. This will relieve the patient’s symptoms and prevent future obstruction and bleeding from the primary tumor.

### INTRAOPERATIVE SURGICAL TECHNIQUE

**Positioning.** For all left-sided colonic resections, it is advisable to place the patient in a modified lithotomy position, which gives access to the anus (eg, for a stapled anastomosis) and allows an assistant or the surgeon to stand between the legs for retraction or an excellent view to mobilize the splenic flexure, respectively. The same positioning obviously also can be used for all
other colon resections, but a supine position usually is sufficient and faster. Laparoscopic procedures typically require the operating table to be tilted and moved to steep Trendelenburg position; appropriate fixation and securing of the patient is therefore mandatory.

**Incision.** For an open procedure, the peritoneal cavity is most commonly entered through a midline laparotomy incision. For a proctocolectomy, we usually recommend the use of an infraumbilical incision in order to provide good exposure for the pelvic dissection. For a more proximal segmental colon resection, however, an equally short but higher midline incision may be more convenient. In addition, a transverse incision or even a subcostal incision may give excellent exposure for a right hemicolecotomy.

For a laparoscopic procedure, a first camera trocar is placed in either Veress needle or in open Hasson technique. The site should be chosen such that additional working ports can be placed along a circle with the target in the center.

**Exploration.** After the peritoneal cavity is entered (open or laparoscopically), the abdomen is explored systematically to determine the resectability of the tumor. Special attention is addressed to the presence of distant metastases in the liver, peritoneal carcinomatosis, or additional synchronous lesions throughout the large intestine. Other accessible organ systems are assessed equally, for example, the gallbladder and the female reproductive organs.

**Colon Resection.** The surgical technique has been standardized for 3 segments: right colon, left colon, and rectosigmoid. Depending on the extent of the resection eventually needed in an individual patient, the technique for those segments may be combined (see Table 49-13). With a detailed description of the maximal resection, that is, an open total colectomy/proctocolectomy, all information about the individual steps necessary to perform any colorectal resection of lesser extent will therefore be provided.

The same steps should be achieved with laparoscopic resections; however, depending on the surgeon’s preference and skills, a medial-to-lateral mobilization of the colon (ie, starting at the feeding vascular stalks before moving to the retroperitoneal attachments) supports the autoretraction of the
colon throughout the critical steps.

On careful exploration of the abdomen, mobilization of the colon starts on the right side. Use of a mobile (eg, Richardson retractor) instead of a fixed (eg, Balfour or Bookwalter retractor) abdominal wall retractor in this first phase will allow a more flexible and unidirectional exposure according to rapidly changing needs. The small bowel is eviscerated from the abdomen and moved to the left. The abdominal wall is retracted to the right side while exerting countertraction on the cecum and ascending colon. A small incision is made at the exposed white line of Toldt to enter the retroperitoneum. Elevating the ascending colon from the retroperitoneal structures, the peritoneum is divided along the lateral gutter from the terminal ileum to the hepatic flexure. On the right side, the ureter is at fairly low risk and routinely falls away; however, special care is needed to avoid damage to the third part of the duodenum. The mobilization is facilitated by firm traction placed on the colon and the surgeon’s left hand inserted into the retroperitoneum as a guide to divide along the peritoneal reflection. Because of the limited view around the hepatic flexure and the presence of small vessels at this level, transsection of the peritoneum with cautery is often advisable.

As the right edge of the gastrocolic ligament is reached, it may be easier to complete the dissection of the hepatic flexure in retrograde direction. The abdominal wall retractor is moved quickly into the upper end of the incision in order to pull in a cephalad direction. The lesser sac is entered far to the left in an avascular portion of the omentum, and the greater omentum is divided inferior to the gastroepiploic vessels between clamps and ligatures. While the omentum may be preserved in benign diseases, its resection with the respective colon segment is part of an oncologic resection. Dissection of the gastrocolic ligament is carried out from the left to the right. Connective tissue attachments between the antrum, duodenum, and transverse mesocolon and the hepatic flexure are divided stepwise by a combination of blunt digital tunneling and sharp dissection using both hands. Care should be taken at this point to avoid dissecting too deeply into the retroperitoneum, where large blood vessels can be encountered. Once the mobilization has been completed around the hepatic flexure, the right colon and transverse colon are attached only to their vascular supply and are ready for resection. This would be used for any standard right hemicolectomy or the first part of an extended transverse colectomy. For total colectomy, mobilization of the whole colon commonly is continued before dividing the major vessels.
At this point, the abdominal wall retractor is moved to the left side of the abdomen, and traction is placed to expose the left portion of the colon. The dissection is initiated at the level of the sigmoid, where the white line of Toldt again is incised and the retroperitoneum entered. Once the areolar tissues are identified, a small sponge is taken, and with firm pressure against the sigmoid mesentery, the retroperitoneal tissues are bluntly reflected, and the left ureter is exposed. Only after the ureter has been clearly identified and moved out of the way is incision of the peritoneum continued into the pelvis for a short distance and up to the splenic flexure along the left gutter. The colon is reflected bluntly from the retroperitoneal tissues, and with firm traction the peritoneal incision is continued. Gentle traction on the transverse and descending colon will help to lower the splenic flexure until it can be visualized fully. A hand placed in the retroperitoneum will help to mobilize the splenic flexure, and under direct vision, the peritoneum over the splenic flexure can be incised. Care must be taken at this point to protect the spleen from direct or traction injury. The final attachments of the splenocolic ligament that hold the splenic flexure are clamped and divided in appropriate tissue portions. Clamping and ligating this tissue are recommended because even small vessels retracting into the left upper quadrant can be a nuisance.

After completion of the first 2 parts, the colon is mobilized completely from its retroperitoneal attachments from the terminal ileum to the upper rectum. Elevation of the colon allows identification of all primary feeding vessels. In order to ligate the inferior mesenteric vessels, the surgeon is on the patient’s left and the colon is reflected to the left. The attachments that run over the sacral promontory and up along the left gutter are incised, and a hand is used to dissect the tissues bluntly from behind the inferior mesenteric vessels. By identifying the inferior mesenteric vessels and making the window just under those, the hypogastric nerves going down into the pelvis are protected routinely. Sometimes, for example, if there is concern about cancer in the rectum or if the patient is very obese, these structures need to be freed up more to elevate the nerves initially and later to dissect them out under direct vision. The avascular window around the origin of feeding vessels then is opened. In the case of the inferior mesenteric vessels, the left hand is placed behind the inferior mesenteric stalk, and the thumb and opposing index finger can clear a window of avascular tissue above it. Dissection of redundant adipose tissue around the vessels is carried out under direct vision, before the vessels are clamped. Before transsection and ligature
of the vessels, the remote location of the ureter is confirmed once more. If the ureter is not identified properly before dividing the vascular pedicle, accidental dissection of the ureter can occur and requires a repair. If unrecognized intraoperatively, the ureter injury may result in a urinoma. In difficult cases (eg, repeat operation or recurrence), it is therefore advisable to place preoperative ureteral stents to allow better identification. The whole vascular stalk may be ligated with a double ligature or a suture ligature. Individual ligature of the artery and vein is optional and has not been shown to provide an advantage. For the reason mentioned earlier, it is recommended to ligate the vessels as proximally as possible, but from an oncologic standpoint a high ligation of the IMA does not provide any advantage in comparison with a low ligature distal to the origin of the left colic artery.248,249

The vascular dissection is then continued around the colonic mesentery. The avascular tissue can be divided sharply while clamping is applied to vessels when they are encountered. The vascular anatomy of the colon is quite variable. However, if one is truly in the retroperitoneum and ligating named vessels at their origin, the colon can be taken out with as few as 3 to 4 clamps. In particular, the inferior mesenteric, middle colic, and ileocolic vessels need to be ligated. The presence of additional right and left colic vessels sometimes requires the use of 5 or 6 clamps. By taking the vessels closer to their origin, that is, before they branch off into multiple subsegments, fewer clamps are necessary and the dissection proceeds more rapidly.

Once the vessels have been ligated, the bowel may be divided by means of cutting linear stapling devices at the previously determined levels. In patients with an underlying disease (eg, ulcerative colitis or FAP), the dissection at this point would be continued as a total mesorectal excision down into the pelvis to the pelvic floor (see respective chapters). It is strongly recommended to have the specimen assessed macroscopically to verify the pathology. Tumor in the resection margin means an inadequate cancer operation requiring a re-resection. Intraoperative frozen sections of the resection margins should be requested whenever there is any doubt about the completeness of the resection.

Recently, there has been much debate on the topic of complete mesocolic excision (CME) with central vascular ligation (CVL), following the principles of total mesorectal excision (TME), allowing for a higher quality
of surgical specimen and a higher number of retrieved lymph nodes compared to conventional colectomy.\textsuperscript{250,251} However, there is no strong evidence that a CME colectomy offers any improved long-term survival benefit compared to standard colectomy.\textsuperscript{251-253}

**Reconstruction/Diversion.** After the resection has been completed, either the bowel ends can be reanastomosed or the proximal end may be brought out as an ostomy. Prerequisites for a successful anastomosis are meticulous technique, well-vascularized and healthy-appearing tissues, apposition of bowel ends without any tension, and good nutritional status of the patient with an albumin level greater than 3.0 mg/dL. Constructing an anastomosis under tension and/or with poor blood supply increases the risk of an anastomotic leak that may cause an infection and sepsis. A protective diverting ostomy does not prevent the leak as such but should diminish the life-threatening complications of an anastomotic leak. While a stapled functional end-to-end anastomosis between the ileum and the colon (ie, an enterocolonic anastomosis) is reasonable, this type of anastomosis may potentially be less desirable between 2 colon segments (ie, a colocolonic anastomosis) because it can result in an iatrogenic giant diverticulum that may interfere with the propulsion of formed stool or impede the performance of a surveillance colonoscopy. Performing an end-to-end anastomosis, either hand-sewn or by means of a circular stapler, will avoid these problems. An ileocolonic anastomosis in most instances can be performed in an unprepared bowel, whereas a colocolonic anastomosis on the left side traditionally requires pre- or intraoperative reduction in the stool load unless a colostomy was performed. As mentioned previously, this view has come under scrutiny.

**Drains.** Placement of drains is more often a matter of personal preference than of scientific objectiveness.\textsuperscript{254-256} Most bowel anastomoses, even colocolonic anastomoses, do not need to be drained. The use of drains generally may be recommended when a pelvic dissection and anastomosis have been performed and accumulation of fluid and blood in the dependent areas around the anastomosis should be avoided. Whether prospective, but underpowered, studies are sufficient evidence to effectuate a change in this practice needs to be determined.\textsuperscript{257,258}

**TECHNICAL CONSIDERATIONS**
**Laparotomy Versus Laparoscopy.** Laparoscopic colon surgery has a clearly established place in the management of both benign and malignant colon diseases. In many specialized centers, it is even regarded the first-line approach unless patient-specific factors suggest otherwise. The path to a nearly unanimous endorsement of the technique at least for right-sided, left-sided, and sigmoid resections for colon cancer started in the early 1990s, moved from palliative resections to institutional case series in curative intent, and culminated in several prospective randomized trials throughout the world, the first large-scale trial being a multicenter study by the NCI. This study, which enrolled 872 patients with stage I to III colon cancer, confirmed that there was a moderate quality-of-life benefit for the laparoscopic approach but otherwise no difference in oncologic outcome and survival between the laparoscopic and open-resection groups. Subsequently, 2 large-scale European prospective multicenter trials (ie, the COLOR [Colon Cancer Laparoscopic or Open Resection] trial with 1248 patients and the CLASICC [Conventional Versus Laparoscopic-Assisted Surgery in Colorectal Cancer] trial with 794 patients) have confirmed similar results. This equality of the study results offered the unique opportunity for both opponents and proponents of the laparoscopic approach to justify their personal preference for either the open or laparoscopic technique depending on their background and skills. In contrast to one early report of a high incidence of port-site recurrences, it has become clear subsequently that with appropriate surgical technique, the incidence is in the range of 0.8% to 1.3% and, on a stage-by-stage comparison, not higher than wound implants after open surgery.

For the laparoscopic procedure, about 3 to 5 trocars are inserted. Lacking the tactile sensation of open procedures, tattooing of the target lesion should generally be performed prior to the surgery. The colon should be mobilized to the same extent as during open surgery, but it may be advantageous to start with the vascular pedicle rather than with the retroperitoneal attachments. The technical equipment to perform an intracorporeal resection and anastomosis is available, but it is questionable whether there is any advantage to this because at some point an incision must be made anyway to retrieve the specimen. In the laparoscopically assisted technique, the segment, once it has been mobilized to the required extent, therefore is exteriorized through a small sleeve-protected abdominal incision, and an extra-abdominal resection
and anastomoses are performed. The bowels are returned into the abdomen, the fascia is closed, and the pneumoperitoneum may be reinstalled to inspect the peritoneal cavity again. To facilitate complex resections, some surgeons use hand-assisted laparoscopic surgery (HALS) to combine tactile sensation with a minimally invasive approach.

**Fluorescent Image-Guided Surgery (FIGS).** The use of fluorescent agents to help guide surgeons intraoperatively is rapidly expanding. Together with the development of suitable endoscopic imaging equipment, this technology is able to help by identifying normal anatomy and minimizing complications.

Iatrogenic ureteric injury is a potentially serious complication of colorectal surgery, with an incidence ranging from 0.7% to 10%. Methylene blue is a fluorescent agent that has been used in patients for many years as a reflectance dye. Intravenously administered methylene blue is excreted renally and concentrated in the urine. It can be excited at 660 nm and emits light typically in the far red/near-infrared region (~700 nm), in which light penetration in tissue is considerably higher than using white light alone. A recent study demonstrated that low-dose intravenous methylene blue was able to identify 10 of 11 ureters intraoperatively when viewed using fluorescence-capable laparoscopes. This technique could potentially be very useful, particularly in challenging procedures where the location of the ureters may not be readily identified under white light visualization alone, for example, in patients with previous radiotherapy or retroperitoneal fibrosis or patients undergoing reoperative surgery.

The use of near-infrared (NIR) laparoscopy together with indocyanine green (ICG) has been investigated to assess the perfusion of bowel anastomosis intraoperatively. In a recent study of 30 patients undergoing colorectal resections, a high-quality intraoperative ICG angiogram was achieved in 29 patients. Anastomotic perfusion was documented as being satisfactory in each successful case and encouraged avoidance of defunctioning stomas in 3 patients with low anastomoses. There were no postoperative anastomotic leaks in this series. This technique is potentially useful as it can identify anastomoses with a poor blood supply that require further proximal re-resection and that would have been missed on white light visualization alone, thereby potentially preventing an anastomotic leak.
SPECIAL CIRCUMSTANCES IN EMERGENCY SURGERY

Approximately 20% of patients with colon cancer present as an emergency requiring an urgent operation for a tumor-related complication (e.g., bowel obstruction, perforation, or massive bleeding). Morbidity and mortality are significantly higher than under elective conditions. Contributing factors are the lack of a mechanical bowel preparation and the patient’s impaired overall status, which typically is characterized by dehydration, third spacing of fluids, anemia, a deranged metabolism with electrolyte imbalances, and possible sepsis. The risks for wound and intra-abdominal infections and anastomotic leakages are 3 to 6 times higher.

Tumor Obstruction. Sixteen percent of patients with colon cancer present with a bowel obstruction and complain of colicky abdominal pain, abdominal distension, vomiting, constipation, and, occasionally, paradoxical diarrhea. Imaging studies (abdominal x-ray or CT scan) characteristically demonstrate the features of a large or small bowel obstruction depending on how proximal in the colon the obstruction is located and whether the ileocecal valve is competent. Attention should be paid to the diameter of the cecum, which presents a risk of cecal perforation if the diameter reaches 12 cm or more. Urgent intervention is required in such circumstances to prevent cecal perforation. The most important differential diagnosis is pseudo-obstruction (Ogilvie syndrome), which is seen as a result of various medical conditions and may mimic the features of bowel obstruction. Every patient therefore should have a rigid proctoscopy, followed by a water-soluble contrast enema, which should visualize only the colon up to the site of obstruction but not beyond the stenosis because the hyperosmolar nature of the contrast material can result in an increase in the intraluminal volume and trigger a perforation.

If the level of obstruction in the colon is proximal enough, a resection with primary enterocolonic anastomosis, for example, right hemicolectomy, extended right hemicolectomy, or subtotal colectomy, may be carried out. If the tumor is located on the left side of the colon, adjustments to the surgical approach are necessary because the stool load proximal to the obstruction is of concern for a colocolonic anastomosis and because that segment of the colon could not be cleared before the operation. Synchronous lesions, which in the setting of an obstructing lesion may occur in up to 15% of patients, may be missed and necessitate further intervention in the future. Strategies
then include either (1) a subtotal colectomy; (2) an on-table lavage with segmental colon resection, intraoperative colonoscopy, and primary anastomosis; or (3) performance of a 2- or even 3-stage procedure instead of the elective 1-stage approach. Historically, obstructed left-sided tumors were treated with a 3-stage approach starting with a defunctioning loop colostomy, followed by resection and anastomosis, and finally by closure of the defunctioning stoma. The Hartmann procedure, the classic example among several 2-stage procedures, consists of a discontinuous rectosigmoid resection with creation of a terminal colostomy and a blind rectal stump in the first stage, followed by a colostomy takedown and reanastomosis in a second operation.

More recently, there has been a trend toward attempting to relieve the acute obstruction at the tumor-bearing segment by colonoscopic insertion of a self-expanding metallic stent. Successful decompression of the prestenotic colon converts the emergency situation into an elective setting, allowing for stabilization of the patient and performance of bowel preparation. The risk of a colonic perforation during stent placement is relatively low but acceptable because an emergency operation would be necessary anyway if the stent could not be placed successfully. Several nonrandomized, noncontrolled case series have demonstrated that colonic stenting for acute obstruction is safe and highly successful.\textsuperscript{275-278} A proximal diversion hence may be avoided with this procedure.

**Tumor-Related Perforation.** Colonic perforation secondary to a tumor occurs in 2 different settings. Either a transmural tumor perforates itself, or the proximal colon becomes overdistended, particularly in the case of a competent ileocecal valve. Both conditions may result in diffuse fecal peritonitis with significant morbidity and mortality. In addition, the tumor perforation results in spillage of tumor cells and thus has to be considered a stage IV tumor. Surgical management is indicated in every case and requires not only addressing the site of colonic perforation but also removing the tumor in an oncologically correct fashion.\textsuperscript{273} The same tactical principles described in the preceding section apply.

**Massive Colonic Bleeding.** Massive bleeding from a colonic tumor is a relatively rare complication. The general algorithms for the workup and management of lower gastrointestinal bleedings apply, but most commonly,
the bleeding site can be easily identified. If the bleeding is minor or self-limited, the standard workup can be performed. If the patient is or remains unstable and requires repeated transfusions, surgical management is indicated.

**MANAGEMENT OF ADVANCED DISEASE**

**Locally Advanced Disease.** It has been estimated that approximately 15% of colonic tumors will be adherent to adjacent organs.

With locally advanced colon tumors, it is still possible to achieve cure if the surgeon is prepared to resect involved adjacent organs. Unfortunately, it is often impossible to distinguish between malignant and inflammatory adhesions, but at least 40% of these adhesions are expected to harbor malignant cells. The surgeon therefore has to consider them malignant until proven otherwise and perform an en bloc resection to achieve a tumor-free margin.

**Operable Metastases.** At the time of presentation, 20% of patients with colorectal cancer have stage IV disease. Distant metastasis, particularly liver and lung, is a major cause of death in patients with colorectal carcinoma. However, patients with asymptomatic liver metastases may have a statistically natural life expectancy of several months up to almost 2 years without any treatment. Chemotherapy and surgical metastasectomy in selected patients may improve disease-free and overall survival substantially, resulting in a cure rate of 30%. In the case of potentially resectable metastases, resection of the colonic primary tumor should be performed in an oncologic fashion.

**Inoperable Disseminated Disease.** In patients with unresectable metastatic disease, the surgical treatment goal is to provide palliation and to prevent predictable complications. In contrast to the oncologically defined standard resections, a limited segmental wedge resection of the colon is acceptable in this setting. In particular, tumors located in the sigmoid colon or in the cecum and ascending colon are suitable for a laparoscopic or laparoscopically assisted resection because these segments can be mobilized easily to a sufficient extent to ensure a safe anastomosis. If a tumor in a patient with metastatic disease is too advanced locally to be resected safely (eg, infiltration of other organs), palliation may be achieved by creating an
internal bypass or a proximal diversion.

**POSTOPERATIVE MANAGEMENT**

Postoperative fast-track management after a colorectal resection has become very straightforward and routine. The immediate postoperative monitoring of vital signs, fluids, and electrolytes, as well as adequate pain control, is not different from any other major surgery. However, there has been an increased emphasis on epidural pain management, early mobilization and regular spirometry exercises, avoidance of tubes and drains (eg, nasogastric tubes), and early resumption of oral intake no later than on the first or second postoperative day with advancement to a regular diet as tolerated. Daily assessment of the abdomen and bowel activity is crucial, including careful auscultation and palpation of the abdomen to assess bowel sounds or peritoneal signs. Unless soaking, a wound dressing may be left in place until the second postoperative day or even for 5 to 10 days if an occlusive transparent dressing is used. The incision has to be checked daily for the presence of induration, hematoma, redness, dehiscence, or discharge of fluids (eg, pus, hematoma, or serosanguineous fluid). Large amounts of serous fluids draining from the wound should not be mistaken for a seroma but indicate a fascial dehiscence until proven otherwise. The average length of stay after colorectal resections depends on the patient’s constitution but generally is in the range between 5 and 7 days for an open standard procedure, and 2 and 5 days for a laparoscopic approach. Before discharge, further tumor treatment should have been addressed with the patient. Adjuvant chemotherapy (and rarely radiation therapy) typically are not initiated before 3 to 4 weeks after surgery and may be delayed if infectious complications or anastomotic leaks occur.

**Complications of Surgery**

The overall perioperative mortality within 30 days of colorectal resections is between 3.5% and 6%\(^{282}\), with less than 2% after elective operations but up to 20% after emergency operations. Complications of surgery may be of a general or surgery-specific nature and can be classified based on the time of their occurrence as either early (within the first 30 days) or late (after 30 days). Intraoperative complications like injury to relevant anatomic structures
such as ureters, spleen, bowel, and duodenum are related to the surgical technique, to blurred anatomic landmarks and layers owing to the disease (eg, peritonitis or massive adhesions), or to the patient’s habitus (eg, obesity). Early surgery-specific complications include bleeding, most frequently within the first few days of the resection, nonspecific infections, or infections related to an anastomotic dehiscence. Other more general complications in the early postoperative period (postoperative days 1-3) commonly are related to the cardiopulmonary system and include pulmonary problems (eg, atelectasis, pneumonia, aspiration, and pulmonary embolism) and cardiac events (eg, arrhythmia, myocardial ischemia, and dysfunction). Insufficient pain control has been recognized as an important factor promoting these conditions because it results in a poor respiratory effort by the patient and the inability to cough up sputum, leading to superficial respiration and suboptimal saturation. Thus, high fever in the 3 days after surgery may be related to the development of an atelectasis rather than to an early infection.

Infectious complications usually occur after the third postoperative day and may be located intra-abdominally, in the wound, in the urinary tract, or in the lungs. The primary workup therefore includes bacteriologic cultures and stains, blood and urine analysis, and a chest x-ray.

Abdominal complications consist of delayed return of upper and lower gastrointestinal function (also referred to as postoperative ileus), fascial dehiscence, and anastomotic breakdown. Clinical leaks occur in 1% to 2% of all colonic resections, but subclinical leaks are more frequent and may be seen incidentally on contrast studies in otherwise asymptomatic patients. A leak may present with insidious symptoms such as fever, tachycardia, abdominal distension, ileus, feces draining through a drain or the wound, or local and generalized peritonitis. Occasionally, a leak may present with sudden deterioration, generalized peritonitis, and septic shock as the result of a significant and rapid contamination of the peritoneal cavity. Due to the heterogeneous symptoms, a leak should be suspected in any patient who is not progressing to the expected degree. Blood parameters such as white blood cell counts and C-reactive protein may be elevated but are nonspecific and difficult to distinguish from a normal postoperative reaction. After an abdominal operation, normal free air should be resorbed within 7 to 10 days. The presence of substantial free subdiaphragmatic air later in the course should therefore raise the index of suspicion for an anastomotic leak.

 Imaging studies to define the presence of an anastomotic leak include a
water-soluble contrast enema to visualize extravasation of the contrast material and/or a CT scan with oral, intravenous, and possibly rectal contrast material. Apart from antibiotic treatment, the management of an anastomotic leak depends on its presumed extent and the clinical presentation. A patient with generalized peritonitis requires a relaparotomy after appropriate resuscitation. Depending on its location, the anastomosis should be taken down and the ends should be exteriorized or, in more favorable conditions, resected, and a new anastomosis performed with healthy-looking bowel ends, either with or without proximal diversion. A local repair alone carries a high risk of failure but may succeed in combination with drain placement and a proximal diverting ostomy. By the time of the reexploration, the prolonged peritonitis in some cases already may have transformed the bowel loops into rigid pipes that would not allow any mobilization for an ostomy or for a new anastomosis. In such a case, creation of a confined leak by means of a catheter enterostomy may be a desperate attempt for local control. A fecal fistula can be managed in a conservative manner if there is no evidence of generalized peritonitis or uncontrolled sepsis. Under favorable conditions, including good nutritional support and absence of a distal obstruction or disease of the involved bowel segment, the fistula may close spontaneously. The surrounding skin will need special care, and a stoma therapist will be helpful in this regard.

Adjuvant Chemotherapy and Radiotherapy

The rationale for adjuvant chemotherapy is based on the fact that we are clearly not as successful with surgical treatment as we would like to be. Fluorouracil (FU) was the first and most extensively evaluated drug for the treatment of colorectal cancer. Multiple studies had been completed without proof of value until Krook’s study. Subsequently, a review of 29 randomized trials concluded that adjuvant chemotherapy for colon cancer resulted in a 5% improvement in survival. When studies using FU-based regimens are analyzed, there is a 2.3% to 5.7% absolute improvement in 5-year overall survival. However, when just those at high risk of recurrence are treated, the improvement in survival in this group is closer to 30%. Patients with stage III colon cancer are recognized to be at high risk for recurrence, and administration of FU/leucovorin (LV) for 6 months after surgery has proven to decrease recurrence and improve long-term survival. The
combination treatment of FU/LV for 6 months was proven to be equivalent in efficacy to 12 months, and the addition of levamisole to FU/LV did not seem to add any benefit.\textsuperscript{287} Low-dose LV also was demonstrated to be equally efficacious as high-dose LV when used in combination with FU. Thus, the first-line standard of treatment from 1998 to 2000 was a combination of FU and low-dose LV (folinic acid) given for 6 months on either a weekly schedule or 5 consecutive days every 4 weeks. At present, there is not enough evidence to recommend the routine use of adjuvant chemotherapy in stage II disease. Lenz and colleagues have demonstrated that molecular or genetic markers may better identify subgroups of patients who are likely to benefit from adjuvant chemotherapy.\textsuperscript{288-290}

Several new agents, for example, irinotecan\textsuperscript{291,292} and oxaliplatin,\textsuperscript{293-295} have demonstrated significantly superior activity in combination with FU/LV in the metastatic setting. Irinotecan/FU/LV (IFL)\textsuperscript{291} and oxaliplatin/FU/LV (FOLFOX) have been entered into randomized clinical trials against FU/LV in resected stage III colon cancer.\textsuperscript{296} Both of these studies prove that the new agents in association with FU/LV were superior to FU/LV alone. Because of these successes, IFL was approved as first-line chemotherapy in 2000. In 2005, FU/LV with oxaliplatin (FOLFOX) was approved for adjuvant therapy and has evolved in most centers as the treatment of choice. The FOLFOX regimen has been compared in a large randomized controlled trial with IFL and irinotecan/oxaliplatin (IROX) in patients with previously untreated metastatic colorectal cancer.\textsuperscript{296} This study showed significantly superior results with the FOLFOX regimen for all end points. The median time to progression observed for FOLFOX was 8.7 months, response rate was 45%, and the median survival time was 19.5 months. The FOLFOX regimen had significantly lower rates of severe nausea, vomiting, diarrhea, febrile neutropenia, and dehydration. Sensory neuropathy and neutropenia were common with the regimens containing oxaliplatin.

Capecitabine (Xeloda), an oral agent designed to generate FU preferentially in tumor tissue, is an exciting new development with improved convenience. A randomized phase III study comparing oral capecitabine versus intravenous FU/LV concluded that capecitabine demonstrated a statistically significantly greater response rate compared with FU/LV (26% vs 17%; \( P < .002 \)) and an equivalent time to progression and overall survival.\textsuperscript{297} This study demonstrated that capecitabine is a suitable alternative
to intravenous FU and perhaps a replacement in the future. Currently, phase II trials are being conducted on capecitabine/oxaliplatin (CAPEOX) and capecitabine/irinotecan (CAPEIRI). 298-302

Two of the most fascinating targets in the treatment of colorectal cancer are the epithelial growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) blockers. 303,304 Agents that inhibit the EGFR or bind to VEGF have demonstrated clinical activity as single agents and in combination with chemotherapy in phase II and III clinical trials. The most promising of these agents are the monoclonal antibodies cetuximab, which blocks the binding of epithelial growth factor, and bevacizumab, which binds free VEGF. 303,304 However, the benefit of cetuximab is limited to patients with a tumor bearing wild-type K-ras, while tumors bearing mutated K-ras do not show any response. 305,306 Both agents have proven benefit and seem to work best as first-line therapy for metastatic colorectal cancer. Introduction into the primary adjuvant treatment after curative resection of stage II and III tumors will remain a subject of future trials. We await future development of these and other newer drugs and their impact in the fight against colorectal cancer.

Generally, radiotherapy does not play a primary role in the adjuvant treatment of colon cancer. However, it may be considered as a locoregional field radiation in selected locally advanced T4N0-N1 tumors. 307,309

**Outcome and Prognosis**

Recent years have produced a trend toward better outcome and survival in patients diagnosed with colorectal cancer. This may be related to safer and more successful surgical treatment in combination with better nonoperative and adjuvant treatments. The perioperative mortality within 30 days of elective colorectal resections is less than 2%, even though it still may be relatively high after an emergency operation, thus resulting in an overall mortality of 3.5% to 5.5%. 282 SEER data demonstrate an overall decline in colorectal cancer mortality. While the overall 5-year survival of patients with colon cancer was at 41% between 1950 and 1952, it has since increased steadily to 63.8% between 1995 and 2000. Analyzed for each stage as defined by the AJCC sixth edition system (Table 49-14) separately, 5-year survival was 93.2% for stage I, 84.7% for stage IIa, 72.2% for stage IIb,
83.4% for stage IIIa, 64.1% for stage IIIb, 44.3% for stage IIIc, and 8.1% for stage IV cancer. The prognosis of patients with synchronous primary colon tumors is not different from that of patients with solitary tumors if they are compared on the basis of the most advanced stage (see Table 49-14).

### TABLE 49-14: FIVE-YEAR SURVIVAL FOR SINGLE AND SYNCHRONOUS COLON CANCER PRIMARY TUMORS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Single (n = 4817; %)</th>
<th>Synchronous by Highest Stage (n = 160; %)</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, I</td>
<td>83</td>
<td>87</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>71</td>
<td>67</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>53</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>14</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

^a By long-rank test.

Data from Passman MA, Pommier RF, Vetto JT. Synchronous colon primaries have the same prognosis as solitary colon cancers, *Dis Colon Rectum* 1996 Mar;39(3): 329-334.

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INTRODUCTION

Laparoscopic surgery has steadily gained acceptance over the past two decades, and now it has replaced open surgery for many abdominal procedures (such as appendectomy and cholecystectomy); it is also becoming the preferred approach to many colorectal procedures (such as colectomy). The reasons for the widespread adaptation of laparoscopic techniques are multiple, as listed in Table 50-1. Laparoscopic techniques, when coupled with enhanced recovery pathways, also allow patients to enjoy a speedier recovery, and are associated with fewer complication rates.

1. Smaller incision
2. Less post-op pain
3. Shorter hospitalization
4. Improved quality of life
5. Shorter posthospital recovery
6. Better cosmetic result
7. Reduction in post-op adhesions

The introduction of hand-assisted laparoscopic surgery (HALS) and the early exposure of trainees to diverse laparoscopic techniques have increased the availability of laparoscopic surgery to more practitioners and patients. Knowledge and experience gained from the evolving laparoscopic practice over the past nearly two decades has provided clarity on indications, contraindications, and technical advancements. This chapter provides a review of the principles behind the practice of laparoscopic colon and rectal surgery. It also provides a brief review of the special considerations for cancer of the colon and the rectum, focusing on providing a contemporary description of the laparoscopic and HALS approaches to segmental resections of the colon and the rectum, and the combined resections of the colon and rectum with creation of pelvic pouches. Finally, a perspective on natural orifice specimen extraction (NOSE), natural orifice transluminal endoscopic surgery (NOTES), and the growing practice of robotic surgery is offered at the conclusion of this chapter.

PATIENT SELECTION

Indications, Contraindications, Evaluations

Laparoscopic surgery can be considered an option for virtually any patient with a colon or rectal condition requiring surgery. With that said, not all patients will be ideal candidates and not all procedures can be performed by all surgeons. All surgeons must find their comfort zone with laparoscopic cases. The initiate to laparoscopy should consider limiting their early practice to right colectomies in patients who are thin and have limited risks of adhesions, as well as benign disease process such as polyps or ileocolonic Crohn’s strictures. Surgeons with advanced skills may be comfortable doing
an entire total proctocolectomy and ileal pouch-anal anastomosis. All of these procedures are technically described in this chapter to provide a range of procedures that are feasible. In addition to the technical range of possibilities, there is a range with respect to which patients will do well with the laparoscopic approach. As with any laparoscopic approach, for example, there would be some cases where a pneumoperitoneum is contraindicated and others where the disease or technical considerations represent contraindications. Indications and contraindications along with pre- and intraoperative evaluations specific to the colon and rectal diseases and patient conditions are provided, followed by focused discussion on oncologic issues relevant to colon and rectal cancer.

**INDICATIONS**

The indications for laparoscopic surgery for conditions of the colon and rectum are predominantly the same as those for open surgery (Table 50-2). For inflammatory bowel disease, the list of indications includes symptomatic failure of medical therapy, dysplasia, and presence of strictures, abscess, and fistula. In acute colitis, urgent subtotal colectomy with end ileostomy may be performed initially as a part of a two or three-stage procedure. Procedures may include strictureplasty, small bowel resection, segmental colonic resection, or proctocolectomy. For diverticulitis, the current American Society of Colon and Rectal Surgeons (ASCRS) guidelines recommend that the decision for elective resection of sigmoid after recovering from acute diverticulitis should be made on a case-by-case basis, and the laparoscopic approach is recommended in selected patients. Large colonic polyps not amenable for resection through the endoscope may be resected through the laparoscopic approach. The laparoscopic approach has been proven to produce equivalent outcomes with open resection for localized colon cancer, when oncological principles are practiced. Faster recovery and fewer postoperative complications are seen with laparoscopic colon resections, thus surgeons who are appropriately trained should use this method. Similar results are found with laparoscopic resections for rectal cancer, though the operations are significantly more difficult, and long-term data with regard to outcomes is still emerging. Robotic surgery has been used for colon resections as well, though its advantages are most accentuated in the pelvis. Some of the technical advantages to robotic pelvic surgery include a stable
camera platform, better visualization, and increased articulation; in skilled hands it is a useful tool. However, it is associated with increased costs and increased operative times. The data supporting the use of robotic surgery are by no means definitive, though the ROLARR (RObotic vs LAparoscopic Resection for Rectal Cancer) trial should help answer whether the robotic approach is better, or at least equal to laparoscopic resection for rectal cancer. Solitary metastatic lesion in the liver with localized tumor in the colon can also be resected laparoscopically in competent hands.

### TABLE 50-2: INDICATIONS IN COLON AND RECTAL DISEASES

1. Ulcerative colitis—refractory disease, dysplasia
2. Crohn’s disease—refractory disease, bleeding, strictures, confined abscess, fistula
3. Diverticular disease—recurrent, noncomplicated
4. Volvulus
5. Colon polyps—not amenable to endoscopic resection
6. Carcinoma colon—localized lesions amenable to 8-cm extraction site
7. Rectal prolapse
8. Rectal cancer (in controlled trials)

The laparoscopic approach is preferred in the repair of rectal prolapse. Resection rectopexy and mesh rectopexy both can be performed through the laparoscopic approach. Laparoscopic rectopexy has similar long-term functional outcomes and low recurrence rates.  

### CONTRAINDICATIONS

General health conditions that would contraindicate a minimally invasive approach requiring a pneumoperitoneum typically include any severe manifestation of organ failure (Table 50-3). Patients with severe chronic obstructive pulmonary disease (COPD), reactive airway disease, or other causes of respiratory compromise are usually not tolerant of pneumoperitoneum necessary for laparoscopic procedures. Patients with advanced cardiovascular disease are also typically intolerant of the
pneumoperitoneum, as it can restrict the fragile dynamics of cardiac output. Finally, patients with end-organ renal failure and severe electrolyte or fluid disturbances and those with liver failure, ascites, or other sources of bleeding disorders are best served with a more controlled, open approach. Sometimes these conditions are not appreciated as problematic until the procedure is under way and the anesthesiologist is experiencing difficulties managing the patient’s hemodynamics. Accordingly, open lines of communication between the surgeon and the anesthesiologist as well as a willingness to convert to open surgery should be the rule and not the exception.
Less absolute contraindications of laparoscopy include the presence of adhesions, cardiac abnormalities, pulmonary gas exchange abnormalities, chronic liver disease, and obesity. None of these are clear-cut or absolute. For example, patients may have several abdominal scars and have undergone numerous prior procedures, even near the site of the anticipated colon.
resection, but they may not have prohibitive adhesions. Unless we know the patient has prohibitive adhesions, we would approach the case laparoscopically with a cautionary note to the patient that the risk of conversion may be higher than 10% to 15%. The same can be said for obesity. Managing obese patients is sometimes facilitated by laparoscopy, such as when the fat is predominantly in the abdominal wall. However, some obesity cases cannot be conducted using laparoscopic techniques—for example, when there is insufficient intra-abdominal space to operate, or when appropriate traction cannot be achieved. In addition, laparoscopic colorectal surgery requires extreme positioning, and an obese patient might be difficult to ventilate in Trendelenburg position and/or might be difficult to position due to the patient’s size/weight.

A final category of absolute and relative contraindications includes those specific to the disease under treatment. For inflammatory bowel disease, a large phlegmonous mass, complex or large abscess, or complex fistulizing disease may not be possible to fully mobilize or to extract the specimen with laparoscopic techniques. Similarly, a toxic abdomen from sepsis or fecal contamination may not be ideal for laparoscopic surgery. Massive dilation of the large or small bowel can prohibit both intra-abdominal visualization and the safe movement of instruments throughout the abdominal cavity. In cases of cancer, there is little evidence in support of tackling large fixed or recurrent tumors through small incisions. The risk-benefit ratio for large, fixed, and recurrent tumors would likely favor open surgery, although it has never been prospectively studied.

PREOPERATIVE EVALUATIONS UNIQUE TO LAPAROSCOPIC SURGERY

A word must be said about the workup of patients who are scheduled for the minimally invasive surgical approach. Although the preoperative evaluations are usually the same as for any other laparotomy approach, it is generally advised that the diagnostic tests for the disease and the treatment be as definitive and clear as possible before laparoscopic surgery. The absence of tactile information demands better preoperative assessments than historically considered necessary for open surgery. This was first realized with tumor staging. The traditional approach with open surgery was to palpate the liver at the time of laparotomy to locate metastatic tumor deposits in the abdomen,
including such sites as the liver, ovaries, peritoneal cavity, omentum, or retroperitoneal lymph nodes. Current imaging with computerized tomography (CT) has improved to the point that such novel findings at surgery are rare. Surgeons may identify small superficial hepatic metastases or peritoneal tumors at the time of surgery, but this is less common than it was when laparoscopic surgery was initiated in the early 1990s.

In a similar fashion, primary tumors need to be well localized prior to surgery. For the most part this can be accomplished by combining endoscopy with tattooing for small, benign lesions, or with CT imaging for large or malignant neoplasms. Endoscopy, although usually accurate, can be misleading because there are no consistent endoluminal landmarks for identifying colonic location. Early experiences with missed lesions and wrong-site resections brought these lessons forward. For malignant lesions it is often possible to see the mass on staging CT scan; this can be very reassuring for accurate localization. In addition to the preoperative testing, we advise that one never leave the operating room without first confirming that the target lesion has been confidently removed and identified in a specimen. Because colonoscopy can misjudge the anatomic colonic location of a lesion by more than one colonic segment, this safety measure seems simple and warranted.

For benign conditions, it is equally important to localize the site of diseased bowel and understand the exact extent of disease. Does the patient have a complex versus simple fistula, or a contained mesenteric abscess versus poorly contained complex or perforated abscess? Of course, the size of the specimen will dictate the size of the extraction site. The larger the lesion to be extracted and the larger the incision, the less the benefit there is to the laparoscopic approach. For Crohn’s disease, CT enterography may help to reveal secondary sites of disease. We would also advise a complete intraoperative assessment of the small bowel in cases of Crohn’s disease, especially in cases of stricturing disease.

**INTRAOPERATIVE EVALUATIONS AND REASONS FOR CONVERSION**

Conversion of laparoscopic procedure to open procedure may be required when difficulties are encountered. The reasons for conversion may include unexpected disease, significant adhesions, and the inability to identify vital
structures such as ureters. It is important to remember that conversion itself is not a complication, even though intraoperative complications necessitate conversion. It should not be viewed as failure but rather as an application of sound surgical judgment. It is probably safer for a surgeon to have a low threshold for conversion, because the timing of conversion is critical to reduce not only overall costs but also complications. A decision to convert is best made early in the procedure, thus avoiding an increased risk of complications and reducing operative time. An early decision to convert will ensure that the rates of morbidity and mortality are maintained at acceptable levels.

For patients who are known to have frail tissues from chronic immunosuppression or other systemic conditions with adverse effects on tissues, extra caution should be taken in handling the bowel in particular but other tissues as well during the surgery. It is more difficult to judge the impact of instruments when there is an inability to use tactile information. For this reason, these cases may benefit from the hand-assisted approach.

A final note should be made about the use of ureteral stents in minimally invasive cases. In general, we would not use ureteral stents for any case that would not be required in the open approach. However, we have a low threshold for placing ureteral stents either preoperatively or during surgery when an inflammatory or tumor process obscures the anatomic location of the either ureter. If they are available and make a difference, the lighted ureteral stents can also be used in the location of the ureter.

**ONCOLOGIC ISSUES SPECIFIC TO LAPAROSCOPIC SURGERY IN COLON AND RECTAL CANCER**

Because of the unique controversies that emerged with the introduction of laparoscopic colectomy for cancer, we offer here a section that specifically covers this topic for both colon cancer and rectal cancer. Soon after the introduction of the laparoscopic colectomy in 1991, a number of concerns regarding the application of this technique in colon cancer arose, including reports of tumor wound recurrences at trocar sites and tumor extraction sites. Such reports were frequent enough that national statements were issued recommending a moratorium on laparoscopic colectomy for cancer outside of clinical trials. In response, a number of randomized clinical trials were initiated simultaneously in North America, Canada, and Europe. At
At least four large prospective, randomized trials have been completed and have reported both short- and long-term outcomes. To date, 3133 patients have been studied by random allocation to laparoscopic versus open surgery and followed for cancer outcomes. These patients are reported from four international trials, including the Barcelona trial\textsuperscript{14} (219 patients), the COST (Clinical Outcomes of Surgical Therapy) trial\textsuperscript{15} (872 patients), the COLOR (COlon cancer Laparoscopic or Open Resection) trial\textsuperscript{16,17} (1248 patients), and the CLASICC (Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer) trial\textsuperscript{18,19} (794 patients). Short-term results from all four studies confirm equivalent mortality and rates of morbidity between the laparoscopic and the open arms. They also consistently demonstrate reductions in length of hospital stay, time to first feed, and time to first bowel movement. Quality of life, although modest, has also been confirmed.

At least three of these trials, the Barcelona, COST, and COLOR trials, have completed 5-year follow-up for the entire cohort of patients. It has been reassuring that these trials have not demonstrated inferiority for the laparoscopic arm with respect to overall survival or disease-free survival. A pooled analysis of all four trials examining 3-year median survival was also conducted, and it confirms the same, that no difference in overall survival or disease-free survival was identified between the open and laparoscopic arms.\textsuperscript{20} Subsequently, a 10-year follow-up of the CLASSIC trial has shown that laparoscopic surgery remains oncologically equivalent to open surgery.\textsuperscript{5} A 5-year follow-up study of the COLOR trial maintains that the oncological outcomes between laparoscopic and open colon surgery are similar.\textsuperscript{21} These data have encouraged the adoption of laparoscopic colectomy for colon cancer in the absence of harm and in the presence of confirmed benefits.

The initial concern with using laparoscopic techniques in colon cancer focused on the potential for abnormal distribution of cancer cells due to the pneumoperitoneum. It was thought that the pneumoperitoneum created a “chimney effect”\textsuperscript{22} that caused a focusing of tumor cells at incision sites, such as trocar or extraction sites, increasing the risk of tumor implants.\textsuperscript{23} There was also at least a theoretical risk that it could cause dissemination of tumor cells through abnormal patterns. This has not been borne out in colon cancer and is not considered relevant, therefore, in rectal cancer. What is considered of relevance in rectal cancer is whether laparoscopic techniques can achieve tumor-free margins with the same rate as open surgery.\textsuperscript{24} It could
be argued that the pelvic dissection is facilitated by laparoscopic equipment and access to the deep pelvis with lighting and visualization superior to open surgery in some cases. However, this has not been proven in diverse practice settings. An additional concern is the ability to achieve distal stapling due to the limits of current instrumentation. The results of the European COLOR II trial indicate that laparoscopic and open surgery are equivalent with respect to local recurrence, and disease-free and overall survival. These issues are also being addressed by a prospective randomized trial conducted by the American College of Surgeons Oncology Group (ACOSOG).

The ACOSOG Z6051 trial is a multicenter, phase III, randomized clinical trial with the primary objective of proving that laparoscopic-assisted resection for rectal cancer is not inferior to open rectal resection, based on composite primary end point of oncologic factors that are indicative of a safe and feasible operation. The end point of this noninferiority trial is based on detailed and standardized pathologic evaluation of the specimen, including circumferential and distal margins and the completeness of the total mesorectal excision. The primary end point is a novel, surrogate end point for long-term oncologic outcome that reduces both the necessary accrual target of the trial and its time to maturation. The secondary end points include patient-related benefits (blood loss, length of stay, pain medicine utilization), 2-year local recurrence, and quality of life. The eligible criteria for the disease include T3N0M0, T1-3N1M0 adenocarcinoma of the rectum with the lower edge 12 cm or less from the anal verge, and completion of 5-fluorouracil (5-FU) or capecitabine-based chemotherapy/radiotherapy in the last 4 weeks. The other patient criteria include age 18 years or greater, ECOG (Eastern Cooperative Oncology Group) performance status 2 or less, body mass index (BMI) 34 or less, no evidence of laparoscopic contraindications, no evidence of systemic disease precluding surgery, nonpregnant, nonlactating, no history of current or previous invasive pelvic malignancy, and no history of psychiatric illness. Surgeon credentialing in both laparoscopic colon and laparoscopic rectal surgery is required for participation in this study. This is based on having completed 20 laparoscopic-assisted resections each of the colon and rectum. The operative reports and the pathology reports of those cases and an unedited videotape of the laparoscopic rectal technique are reviewed by two designated investigators. This noninferiority trial funded by the National Cancer Institute (NCI) is projected to enroll 650 eligible patients in the United States and
Canada. Further details and contact information can be obtained from the following website: http://www.cancer.gov/clinicaltrials/ACOSOG-Z6051.

**Key Points**

1. Accurate preoperative assessment of disease extent is a prerequisite to make the procedure successful.
2. Preoperative tattooing of the lesion with colonoscopy will aid in the localization of the tumor during the procedure.
3. Dense adhesions or extensive disease that prevents accurate identification of the vital structures and increases the risk of complications should cause the surgeon to convert early to an open procedure.
4. Care should be taken during handling of bowel in patients, particularly on high-dose steroids, due to increased fragility of the tissues. Atraumatic graspers or the HALS approach is preferred to avoid direct grasping of the colon.
5. Placement of a ureteral stent should be considered when there is difficulty in locating one or both ureters as a result of inflammation or tumor in the retroperitoneum.
6. In cases of malignancy or dysplasia, it is essential to perform a complete oncological resection. This includes adequate mobilization, high vascular ligation, satisfactory lymph node harvest, and negative resection margins. Intracorporeal ligation is required to achieve high vascular ligation.

**GENERAL TECHNICAL INFORMATION**

**Equipment and Instruments**

Basic laparoscopic equipment is common for most of the cases and is detailed in the previous chapters (Table 50-4 and Fig. 50-1). Surgeon acquaintance and comfort with the equipment is more important than the exact specifications. A 30-degree laparoscope is more useful than the 0-degree laparoscope, particularly for visualization during mobilization of the flexures and working in the pelvis. Trocars should have the ability to be sutured or have stability threads to prevent dislodgement or leakage during
the case. The cautery attachment should be on the upper side of the instruments so it does not interfere with hand movements during dissection or slip off as a result of gravity and repeated hand movements. Monitors, light source, camera unit, and CO\textsubscript{2} insufflator should all be placed on readily mobile units to allow easy positioning and provide the surgeon with better ergonomics. Dedicated laparoscopic operating rooms with multiple monitors, and dedicated laparoscopic towers are increasingly being used. Bowel handling graspers should be atraumatic in order to prevent serosal injury. The Babcock forceps are best applied alongside the bowel, on the mesentery, or on the opposing peritoneal surface. The atraumatic alligator bowel grasper can supplement the Babcock graspers while mobilizing the bowel because of its large surface area.

**TABLE 50-4: COMMONLY USED LAPAROSCOPIC INSTRUMENTS**

1. Video camera unit
2. Light source
3. CO\textsubscript{2} insufflator
4. 30-degree laparoscope (5 or 10 mm)
5. Suction/irrigator
6. Cannulas (Hassan and 10/12 or 5 mm)
7. Scissors with cautery attachment
8. Babcock graspers
9. Intracorporeal vascular ligation device
10. Circular stapler for pelvic cases
11. Linear stapler (optional)
12. Automatic clip applier (optional)
13. LigaSure (optional)
14. Harmonic scalpel (optional)
Although some might prefer the Veress needle for insufflating, we prefer the Hassan-type cannula and open insertion technique as they minimize the risk of injury to intra-abdominal structures. Instruments should be of sufficient length to reach up to the flexures and down into the pelvis from centrally located ports; this minimizes the need for extra ports. Total proctocolectomy and abdominal perineal resection (APR) procedures in particular require long instruments that are at least 38 to 40 cm. Care should
be taken with the use of energy devices (electrocautery and ultrasonic cutting
devices) to minimize the risk of complications from the exposed metal
components of the tools. The curved scissors allow more maneuverability,
and the ability to cauterize with the curved scissors can save time.

SPECIAL DEVICES IN COLON AND RECTAL
LAPAROSCOPIC SURGERY

Several options are now available for handling the colon mesentery. The
automatic clip applier can be useful for dissecting the mesenteric vessels or
controlling small to medium-size bleeding vessels. LigaSure (ValleyLab,
Boulder, CO) is used to fuse tissue bundles and vessels up to 7 mm diameter
using a combination of pressure and thermal energy. The Harmonic scalpel
utilizes ultrasonic energy in cutting and coagulating the tissues
simultaneously and offers better precision. The laparoscopic linear stapler can
serve a dual purpose, as it allows transection of the colon without
contamination and a vascular load can be used to transect a vascular pedicle.
Special maneuvers with the linear stapler aid in the preparation of J-pouch
and making of side-to-side anastomosis. Circular anastomotic stapler is used
for making colocolic or ileocolic anastomosis.

PATIENT POSITION AND ROOM SETUP

Careful positioning and securing of the patient on the operating table is
essential for safety of the procedure because steep inclinations of the
operating table are required to assist in achieving proper exposure of the
operative field. For the supine position, ankle straps ensure that steep
Trendelenburg position is tolerated. and shoulder straps or bean bags can
ensure that the patient does not shift side to side when the table is tilted to the
left or right. For synchronous cases, having the lower extremities secured in
stirrups creates the same effect as ankle straps. For most cases, it is ideal to
have the arms securely padded and strapped to the sides of the table.
Generous padding at the elbow and neutral positioning of the wrist will
minimize the risk of ulnar or median nerve injury, respectively, from pressure
during long-duration surgery. A urinary catheter decompresses the bladder
and an orogastric or a nasogastric tube decompresses the stomach to avoid
inadvertent injury and to maximize space in the abdominal cavity. The
The surgeon and the surgical assistant stand on the patient’s side with the monitor on the opposite side to achieve consistent and in-line orientation of the field. The surgeon’s eyes, hands, trocars, instrument tips, and monitor should all be directly parallel and closely aligned to minimize the difficulties associated with reverse image operating (Fig. 50-2).

**FIGURE 50-2** Position of equipment and the surgical team for laparoscopic right hemicolectomy. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

**PORT PLACEMENT TECHNIQUE**

A cut-down technique is used to insert Hassan’s trocar, with Hassan’s
cannula as the first port. Pneumoperitoneum is achieved by insufflation of carbon dioxide to 12 to 14 mm Hg. A 30-degree laparoscope is the preferred camera as it offers the optimal operative view. The rest of the ports are inserted under direct visual guidance.

**WOUND CLOSURE**

Trocars are removed after the pneumoperitoneum is fully released through the cannulas to avoid sucking of the bowel into the port sites and to avoid the concentration of tumor cells at the trocar sites in cancer cases. The 5-mm port sites do not require fascial closure unless there is significant enlargement of the fascia during the procedure. Port site closure should include peritoneum and fascia when they are 10 mm or greater. The lateral ports are closed under direct visualization prior to closure of midline wounds. The “Endo Close” spring-loaded suturing device can be used to close the incision. The fascia is closed with a figure-of-eight suture and an extracorporeal knot is tied. A purse-string suture is an option for closing the periumbilical site.

**Right Hemicolecystomy**

**STEP 1: PATIENT POSITION AND ROOM SETUP**

The patient is carefully positioned supine and secured on the operating table as described previously. The surgeon and the surgical assistant stand on the patient’s left side with the monitor on the right side to achieve consistent and in-line orientation of the field. The instrument table is easily accommodated at the foot of the bed and the scrub nurse on the patient’s right side.

**STEP 2: PORT PLACEMENT AND EXPLORATION**

A 10 to 12 mm port is placed in the supraumbilical area using an open cut-down technique. A different site is preferred (typically left upper quadrant [LUQ]) when a midline scar is present and extensive adhesions are anticipated. A 30-degree camera is passed through this port, and under direct vision two 5-mm trocars are placed—one in the LUQ lateral to the epigastric vessels and 2 cm below the costal margin, and the other in the suprapubic midline (Fig. 50-3). As an alternative, one can place three 10- to 12-mm
trocars; this allows maximum flexibility for placement of instruments and the camera, but the more experienced surgeon may exchange one or more for 5-mm trocars.

**FIGURE 50-3** Position of laparoscopic instruments for right hemicolecotomy. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)
Simple adhesions encountered at this stage should be divided. Then, an inspection of the abdominal cavity should be performed to confirm the pathology for which surgery was indicated and to exclude other pathology. The presence of a locally adherent or bulky tumor should be approached with a conversion to open surgery. The liver is carefully inspected for metastatic disease. If resectable metastases are identified, we would convert to open surgery. Some surgeons are comfortable with laparoscopic removal of hepatic metastasis or choose to address this at subsequent surgery. Alligator or Babcock graspers are preferred to raise each liver lobe to view all surfaces. The peritoneal surfaces should then be inspected to exclude metastases. In cases of Crohn’s disease, the entire small bowel should be inspected for secondary sites of disease not detected by preoperative imaging.

**STEP 3: MOBILIZATION OF THE CECUM**

The patient is placed in a steep Trendelenburg position, with the right side of the table inclined upward. The 30-degree laparoscope is deployed through the LUQ port. The pelvis is viewed to ensure that the small bowel loops can be moved up into the upper abdomen; in the absence of adhesions it is often simplest to sweep the mesentery of the bowel along with the bowel into the left upper quadrant. Right lower quadrant (RLQ) adhesions are not uncommon due to the prevalence of hysterectomy, oophorectomy, and appendectomy procedures in the general population. Presence of significant adhesions in the pelvis (eg, inability to extract terminal ileum from the pelvis) is an indication for early conversion to open procedure at this point, as full exteriorization will not be possible later.

The next step is to identify the right ureter at the pelvic brim, where it runs over the bifurcation of the common iliac artery (**Fig. 50-4**). In an obese patient, the ureter is identified after opening the peritoneum. It is important to be patient and wait to observe peristalsis in the ureter to avoid mistaking the psoas tendon or the gonadal vessels for the ureter. The cecum is then pushed or gently grasped with a Babcock from the supra umbilical port and elevated medially and toward the head. The peritoneum around the base of the terminal ileum and the cecum is then opened with the scissors through supraumbilical port, and correct retroperitoneal plane is entered. Using a grasper on the cut peritoneal edge and not on the bowel, the right lateral peritoneal reflection is opened along the white line of Toldt toward the
hepatic flexure. Care should be taken to initially divide only the superficial layer of the peritoneum. As the dissection proceeds toward the hepatic flexure, the pneumoperitoneum helps separate the tissue planes. The plane between the colon mesentery and the Gerota fascia is then developed using a combination of blunt dissection and cautery, and care must be taken to avoid dissection behind the kidney.
The peritoneum on the medial side of the terminal ileum should be incised to allow full mobilization of the cecum. Upward tension should be applied on the peritoneal fold medial to the terminal ileum, and incision is made in the superficial peritoneal layer alongside the pelvic brim superior and parallel to the right iliac artery. The dissection is continued up to the level of the duodenum. Then the lateral dissection is advanced medially with care until the inferior vena cava inferiorly and duodenum superiorly. These two structures indicate the achievement of sufficient dissection.

**STEP 4: MOBILIZATION OF THE HEPATIC FLEXURE**

The patient is now placed in reverse Trendelenburg position with the right side steeply inclined upward. The laparoscope is shifted into the suprapubic port, and the surgeon and the assistant trade positions. The hepatocolic ligaments are grasped just cephalad to the colon and traction placed obliquely to elevate the tissues toward the anterior abdominal wall and inferiorly. The hepatocolic ligament is divided with electrocautery scissors or an ultrasonic dissector, as preferred. Blunt dissection is then performed to separate the underlying tissue from the peritoneum. Occasionally larger vessels encountered require clips. The dissection is then continued along the gastrocolic ligament, identifying the plane between this and the transverse mesorectum, until the level of falciform ligament is reached. Care should be taken during this dissection not to damage the duodenum as the hepatic flexure is mobilized off the retroperitoneum in the right upper quadrant (RUQ) (Fig. 50-5). At this point, the whole right colon is mobilized to the midline and the right retroperitoneum is exposed, allowing visualization of the duodenum, Gerota fascia, and right ureter.
STEP 5: VASCULAR DIVISION

Vascular ligation and division of the mesenteric vessels can be performed either by intra or extracorporeal method. The surgeon and the assistant are back to original positions with the laparoscope placed through the LUQ port. The intracorporeal method should be used for obese patients, as it is difficult to exteriorize the ileocolic pedicle. Intracorporeal ligation is preferred for the malignant diseases to ensure proximal ligation of the vessels (Fig. 50-6). Upward tension is applied on the right colon to display the ileocolic and right
colic vessels, and once mesenteric windows are created, the vessels are ligated with hemoclip, Endoloop devices (Ethicon, Cincinnati, OH), or a linear vascular stapler. It is important to visualize or palpate the junction of the ileocolic and superior mesenteric vessels to provide proximal resection of lymphatics in cancer cases without compromising blood flow to the rest of the small bowel.

**FIGURE 50-6** Intracorporeal division of vasculature of right colon. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

**STEP 6: EXTERIORIZATION**

Once intracorporeal ligation has been completed or if extracorporeal ligation has to be performed, the table is returned to a neutral position. A Babcock grasper is placed through the suprapubic port and applied to the appendix or ligament of Treves or the mesentery of the cecum. The pneumoperitoneum is vented out through the ports and the camera equipment removed. Then a
small (4-6 cm) vertical incision is made for purposes of colon exteriorization; typically it is more cephalad than caudal to the umbilicus. The wound edges are protected with a wound guard and then the bowel is exteriorized with the help of Babcock grasper left already at the level of the cecum. The right colon is exteriorized from the terminal ileum to the transverse colon (Fig. 50-7). It is generally not necessary to have divided the omentum intracorporeally as it can also be exteriorized through the incision unless it is bulky. Once the bowel is exteriorized, vascular ligation is performed in a standard manner.
FIGURE 50-7 Exteriorization of right colon. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

STEP 7: ANASTOMOSIS

The mesenteric and bowel division, vascular ligation if appropriate, and anastomosis can be completed after exteriorization in an identical way to
standard laparotomy. This degree of mobilization allows for a handsewn end-to-end anastomosis or a wide, stapled side-to-side anastomosis. Following anastomosis, the bowel is gently returned into the abdominal cavity. Irrigation of the abdominal cavity is performed at this time. The irrigation process is conducted through the open wound and can make use of standard suction devices without the need for the laparoscopic suction irrigator equipment. The aspirate from the irrigation process is inspected to determine whether it is clear or bloody. If the aspirate is blood-stained, the abdomen may need to be reevaluated by reestablishing the pneumoperitoneum. In our experience, it is rare to have to reinspect using the pneumoperitoneum. By using Harrington-type retractor, inspection through the periumbilical incision allows for visualization of the port sites as the trocars are removed. Copious irrigation of all the wounds is then performed. The incisions are closed in two layers: fascia and skin.

Alternative Technique for Right Hemicolecotomy

An alternative technique, in which the dissection starts from the medial aspect and extends laterally, is also practiced for right hemicolecotomy. The dissection commences with the opening the peritoneum of right mesocolon. This allows for the mobilization of the colon with minimal manipulations. The right colic and ileocolic vessels are identified first and ligated using clips or vascular stapler. Then the peritoneal incision is extended superiorly toward the transverse colon, and then the dissection continues along the transverse colon inferiorly and along the hepatic flexure, ascending colon, and cecum medially. After the colon is freed from the peritoneal attachments on the medial side, the dissection continues along the white line of Toldt, starting from the cecum to the hepatic flexure and the transverse colon (Fig. 50-8). The right colon is detached from all the attachments and is then brought outside from the extended skin incision at the umbilicus. Then the right colon is resected extracorporeally and ileocolic anastomosis is performed as described in the previously mentioned method.
**Left Hemicolecctomy**

The left hemicolecctomy procedure is similar to the right colectomy, only in mirror-image reverse. One major difference is the care that must be taken around the spleen. The hand-assisted approach can facilitate management of the splenic flexure and therefore it is described as an alternative approach.

**STEP 1: PATIENT POSITION AND ROOM SETUP**

Positioning and securing of the patient on the operating table is done in a similar fashion as right hemicolecctomy. The surgeon and the surgical
assistant stand on the right side with the monitor on the left side and parallel in-line orientation is maintained. The instrument table is accommodated at the foot of the bed and the scrub nurse is on the patient’s left side.

STEP 2: PORT PLACEMENT AND EXPLORATION

A four-port technique is used, with ports in the supraumbilical area, suprapubic area, right upper quadrant, and left lower quadrant (LLQ) (Fig. 50-9). Simple adhesions encountered at this stage should be divided. Then a careful inspection should be performed to confirm the pathology and any presence of additional disease. Conversion to open procedure should be made for the same conditions and indications as described for the right colectomy.
STEP 3: MOBILIZATION OF THE LEFT COLON

The patient is placed in a steep Trendelenburg position, with the left side of the table inclined upward, and the small bowel loops are swept to the right side of the abdominal cavity using the graspers. The left ureter is identified before proceeding with the dissection. The dissection commences lateral to
the proximal sigmoid colon. The peritoneum is incised and then dissected along the white line of Toldt toward the splenic flexure (Fig. 50-10). The plane is developed carefully, avoiding kidney injury, between the colon mesentery and the Gerota fascia. Then the lateral dissection is advanced medially until the aorta is reached.
STEP 4: MOBILIZATION OF THE SPLENIC FLEXURE

The patient is now placed in reverse Trendelenburg position with the left side steeply inclined upward. The surgeon standing between the legs of the patient and the assistant on the right side with in-line arrangement of camera, monitor, and the instruments provide better surgical ergonomics. The instruments are repositioned with grasper through the suprapubic port and the cutting instrument through the left lateral port. The assistant grasps the greater omentum superior to the distal transverse colon through the right lateral port and retracts upward toward the abdominal wall cranially (Fig. 50-11). With the countertraction, the surgeon incises the peritoneum and enters the lesser sac. The dissection is then advanced parallel to the transverse colon to open up the lesser sac and mobilize the transverse colon. The dissection is then advanced toward the lateral dissection so that the splenic flexure is completely mobilized to the level of the umbilicus.

FIGURE 50-11 Mobilization of splenic flexure. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)
STEPS 5–7: VASCULAR DIVISION, EXTERIORIZATION, AND ANASTOMOSIS

Vascular ligation and division of the mesenteric vessels are performed either by incorporeal or extracorporeal method. The colon is exteriorized through the 4- to 6-cm midline vertical incision and anastomosis is performed in a similar fashion as in right hemicolecctomy.

HAND-ASSISTED LAPAROSCOPIC SURGERY

Hand-Assisted Laparoscopic Left Hemicolecetomy

STEP 1: PATIENT POSITION AND ROOM SETUP

The patient is positioned and secured on the operating table in a similar fashion as for a laparoscopic-assisted procedure.

STEP 2: PORT PLACEMENT AND EXPLORATION

Lower midline incision is made below the umbilicus. The hand port should be placed in such a position where the nondominant hand acts like a laparoscopic retractor. The incision size should be one-half size smaller than the operator’s hand size, and the incision length should remain the same through all layers of the abdomen to avoid leakage of air around the hand port (Fig. 50-12). Gelport is the new generation of multifunctional hand port that allows the usage of hand, laparoscope, and laparoscopic trocars, and maintains an airtight seal when the hand is removed. The surgeon’s hand through the hand port guides the insertion of the 30-degree laparoscope in the periumbilical region. A 5/10-mm port for scissors with cautery is made in the LLQ under laparoscopic visualization (Fig. 50-13).
FIGURE 50-12 Position of hand following insertion through hand port. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)
FIGURE 50-13  Position of incision for hand port and laparoscopic ports for left hemicolecctiony. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

STEP 3: MOBILIZATION OF THE LEFT COLON AND SPLENIC FLEXURE

Traction is achieved when the hand and the colon is dissected in the similar
fashion described previously for the laparoscopic hemicolecctomy (Figs 50-14 through 50-16). A grasper can be introduced through a 5-mm cannula in the RLQ to achieve additional traction for adequate mobilization of the spleen.

FIGURE 50-14 Hand-assisted mobilization of left colon. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)
FIGURE 50-15  Hand-assisted mobilization of splenic flexure—omental attachments. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)
FIGURE 50-16  Hand-assisted mobilization of splenic flexure. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

**STEPS 4–6: VASCULAR DIVISION, EXTERIORIZATION, AND ANASTOMOSIS**

Vascular ligation and division of the vessels is typically performed using intracorporeal techniques. The colon is exteriorized through the hand port and divided, and anastomosis is performed with either handsewn technique or standard stapled method.

**Sigmoid Colectomy**

**STEP 1: PATIENT POSITION**

The patient is placed and secured on the operating table in modified lithotomy position the same as for left hemicolecction. The surgeon and the
surgical assistant stand on the right side of the patient, and the camera, trocars, and monitor are aligned parallel to minimize reverse-image operating.

**STEP 2: PORT PLACEMENT AND EXPLORATION**

The laparoscope is inserted through the supraumbilical port and the trocars are placed under visualization in suprapubic, right, and left lower lateral positions (Fig. 50-17). The abdominal cavity should be inspected with confirmation of the indicated pathology and other pathology excluded, as previously described.
Step 3: Mobilization of the proximal sigmoid and descending colon
The patient is placed in steep Trendelenburg position with the left side of the table inclined upward. The 30-degree laparoscope is deployed through the supraumbilical port and the small bowel loops are swept to the right side. The left ureter is identified at the pelvic brim. Conversion to an open procedure is necessary if the ureter cannot be identified confidently. The ureter is swept down and away in order to avoid injury during ligation of the mesenteric vessels. The dissection commences lateral into the left ureter by incising peritoneum lateral to the sigmoid colon. The dissection continues along the white line of Toldt toward the splenic flexure in the same manner as done for left hemicolecctomy. Mobilization of splenic flexure is performed as required.

**STEP 4: MOBILIZATION OF THE DISTAL SIGMOID COLON AND UPPER RECTUM**

After mobilizing the descending colon completely, the dissection is now directed caudally. With the retraction of the sigmoid colon cephalad and medially, the peritoneal incision is then extended distally to the midrectum entering the presacral space. The left ureter and the iliac vessels are identified and protected throughout this part of the procedure (Fig. 50-18). The presacral space is developed by the division of the fine adhesions and care should be taken to protect hypogastric nerves by sweeping them backward toward the sacrum.
STEPS 5 AND 6: VASCULAR LIGATION AND EXTERIORIZATION

The sigmoid colon is elevated anteriorly and inferiorly to expose the mesenteric vessels. Then incision is made in the avascular plane on both sides of the vessels. The superior hemorrhoidal and sigmoid vessels are isolated and ligated at the level of aortic bifurcation using vascular staplers, clips, or Endoloop devices (Fig. 50-19). We ligate just distal to the takeoff of the left colic vessel. Some surgeons express a preference for ligation at the origin of the inferior mesenteric artery, proximal to the left colic branch. The sigmoid becomes more mobile after the ligation of the vascular pedicle. The upper rectum is then divided using a linear cutting stapler (Fig. 50-20).
FIGURE 50-19 Intracorporeal vascular division of superior hemorrhoidal and sigmoidal vessels. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)
Then the pneumoperitoneum is vented out via the laparoscopic ports. The divided sigmoid colon is brought out through the extension of the LLQ incision. The proximal colon is divided at the sigmoid and descending colon junction.

**STEP 7: ANASTOMOSIS**

A purse-string suture is inserted around the colon that is tied around the anvil of the staple gun inserted into the lumen. Then the colon is returned to the abdominal cavity. The peritoneal cavity is irrigated and checked for blood, and the fascial defects are closed. After the reinsufflation of the abdominal cavity, the stapling device is introduced through the anus. The anvil attached...
to the shaft of the stapling device is advanced across the staple line under direct visualization. The anvil is attached to the gun, approximating the bowel ends, and then the device is fired. The anastomotic integrity and hemostasis can then be assessed using a proctoscope. The pneumoperitoneum is released after withdrawing cannulas under direct visualization.

The alternative approach is to perform a handsewn anastomosis through a small lower midline incision of 5 to 6 cm. After bowel exteriorization, the bowel is excised and end-to-end anastomosis is performed, taking care to ensure proper alignment of the mesentery.

**Hand-Assisted Laparoscopic Sigmoidectomy**

The patient is positioned in the same way as for the laparoscopic-assisted approach. The hand port is placed in the lower midline incision in the lower abdomen 1 cm above the pubic symphysis. The incision size should be one half-size smaller than the surgeon’s hand to maintain effective pneumoperitoneum. Then the surgeon’s left hand in the gel port guides the placement of other trocars. A 30-degree laparoscope is placed in the supraumbilical port and cautery attached to the scissors is placed in the RLQ port. The surgeon, standing on the left side of the patient, uses the left hand to provide retraction of the sigmoid colon while the cautery is operated with the right hand. The diseased specimen is extracted through the incision made for the hand port, and extracorporeal division of the vasculature can be performed. The anastomosis is made using the stapling device in the same manner as described previously. The pneumoperitoneum is reinstated, and the abdominal cavity is irrigated and inspected for hemostasis. Then the anastomotic site is inspected for leakage. Normal saline is placed in the abdomen and pelvis such that the anastomosis is submerged. A noncrushing clamp is placed proximal to the anastomosis and the rectum is then insufflated using a flexible sigmoidoscope. If bubbles are detected, either the anastomosis needs to be repaired at the site of the leak or the case needs proximal diversion with an ileostomy. Then the abdomen is closed after venting the pneumoperitoneum.

**Transverse Colectomy**
STEP 1: PATIENT POSITION AND ROOM SETUP
The patient is placed and secured well on the operating table in supine or modified lithotomy position, depending on whether the pathology is closer to the right or left colon, respectively.

STEP 2: PORT PLACEMENT AND EXPLORATION
The laparoscope is inserted through the supraumbilical port, and two cannulas are inserted in the right and left lower quadrants under direct visualization. The surgeon shifts sides depending on the mobilization of the hepatic flexure or the splenic flexure.

STEP 3: MOBILIZATION OF THE HEPATIC FLEXURE
Dissection and mobilization of the hepatic flexure is performed as described under right hemicolectomy.

STEP 4: MOBILIZATION OF THE SPLENIC FLEXURE
Dissection and mobilization of the splenic flexure is performed as described under left hemicolectomy.

STEP 5: MOBILIZATION OF THE TRANSVERSE COLON
The stomach is lifted up, and with retraction of transverse colon downward the omentum is divided. Thus the transverse colon is freed from its attachments on either side.

STEPS 6–8: VASCULAR DIVISION, EXTERIORIZATION, AND ANASTOMOSIS
The vascular pedicle is divided intracorporeally, and the mobilized transverse colon is exteriorized through the extended incision in the supraumbilical area. Care should be taken around the vascular pedicle of the transverse colon. The middle colic vessels are quite short, and the vein branches easily tear and cause difficult bleeding. Too much traction on these vessels can result in disruption of venous branches and significant bleeding. The bowel is then
divided and anastomosis of the free ends is done with handsewn technique or standard stapled technique.

**TECHNICAL PROCEDURES FOR RECTAL DISEASES**

Anterior resection, or sometimes referred to as a high anterior resection, is a surgical procedure used for resection of tumors or pathology present in the proximal rectum or distal sigmoid (>12 cm from the anal verge). In contrast to the anterior resection, the low anterior resection is used to treat tumors or pathology in the mid- to distal rectum, and an ultralow anterior resection is a sphincter-preserving approach where the anal canal is spared and a coloanal anastomosis or ileal J-pouch anastomosis is performed. APR is a two-part procedure that involves an abdominal and pelvic procedure where the rectum and colon are mobilized along with a perineal procedure where the rectum and the anus are resected. With this procedure, the patient is left with a permanent colostomy. An APR is required for tumors within 1 cm of the top of the anal canal (Fig. 50-21).
Rectopexy, or repair of rectum, is typically combined with sigmoid resection but can be performed by itself for treatment of rectal prolapse. We
typically perform a sigmoid resection and colorectal anastomosis; also, we secure the lateral parts of the rectum to the presacrum to generate additional fixation.

**Anterior Resection**

**STEP 1: PATIENT POSITION AND ROOM SETUP**

The patient is placed in modified lithotomy position or synchronous position and securely strapped to the operating table. The setup is similar to that for sigmoid colectomy.

**STEP 2: PORT PLACEMENT AND EXPLORATION**

A four-port technique is used in which trocars are positioned at supraumbilical, suprapubic, and right and left lower quadrants. The abdomen is inspected to confirm the pathology and rule out metastases. Estimation of lower margins of the rectum and the pathology is crucial to decide the procedure in advance of conducting the operation.

**STEP 3: MOBILIZATION OF THE LEFT COLON AND SIGMOID COLON**

Dissection of the left colon and the sigmoid colon is carried out in a similar fashion as explained in the sigmoid resection.

**STEP 4: VASCULAR LIGATION**

For cancers, the vascular pedicle needs to be taken proximal, incorporating at least the superior hemorrhoidal and sigmoidal vessels. A vascular stapler, LigaSure, or a Harmonic scalpel can be utilized for intracorporeal ligation. Both ureters should be visualized and moved out of harm’s way prior to vascular pedicle ligation. The left ureter courses close to the sigmoidal and hemorrhoidal vessel in the retroperitoneum above the pelvic brim. For nononcologic pathologies, vessels can be ligated at more distal locations. Extracorporeal ligation of the vessels is an alternative if adequate exposure can be obtained through the extraction site.
**STEP 5: MOBILIZATION OF THE RECTUM**

After vascular ligation, the presacral space is entered to start the dissection of the rectum. The ureters should be identified to avoid injury to them. Presacral nerves are carefully protected by gently sweeping them down and away from the dissection plane. The dissection continues laterally on either side until it meets posteriorly, developing a presacral plane (see Fig. 50-18). The rectum is mobilized by creating a plane anteriorly between the rectum and seminal vesicles and prostate in men, and between rectum and posterior vaginal wall in women. Complete mesorectal excision along with distal and circumferential clearance is the key factor for achieving complete oncologic resection. For cancers, the level of rectum for the site of transection is marked using ink tattoo preoperatively, and this is visualized at the time of the surgery with endoscopy. The level of transection is typically identified and tattooed before starting neoadjuvant chemoradiation for patients requiring it.

**STEP 6: EXCISION OF THE RECTUM AND EXTERIORIZATION**

The rectum is excised at the marked position with the linear stapler gun (see Fig. 50-20) and then the specimen is extracted out through the extended incision in the supraumbilical region. The proximal end of the specimen is then dissected extracorporeally and the remaining colon reintroduced with the anvil of the stapler gun held by the purse-string sutures.

**STEP 7: ANASTOMOSIS**

The anastomosis is performed in a fashion similar to what was described for sigmoid colectomy and low anterior resection using the circular stapler. The integrity of the anastomosis is always checked prior to closing the abdomen. Conversion is rarely needed when the anastomosis is at this high level, and is typically reserved for circumstances where the tissue is of poor quality.

**Low Anterior Resection**

**STEP 1: PATIENT POSITION AND ROOM SETUP**

The patient is placed in the combined synchronous or modified lithotomy
position and secured well on the operating table. The thighs can be kept more at the level of abdominal wall to avoid interference with the laparoscopic instruments used in the lower ports. The surgeon stands on the right side of the patient and faces toward the LLQ of the patient. The surgeon may have to shift to between the patient’s legs if mobilization of the splenic flexure is required. The surgeon’s assistant stands on the right and the scrub nurse on the left. The camera positioned to the left of patient’s hips in the beginning is moved cephalad as the mobilization of the sigmoid colon and descending colon continues.

STEP 2: PORT PLACEMENT AND EXPLORATION

A 30-degree laparoscope is introduced through the supraumbilical position. Under direct visualization, three 5-mm trocars are in suprapubic position, right lower lateral quadrant, and left lower lateral quadrant positions (see Fig. 50-17). Lower quadrant trocars are inserted lateral to the epigastric vessels.

STEP 3: MOBILIZATION OF THE LEFT COLON

The patient is placed in the steep Trendelenburg position with the left side of the abdomen inclined upward. The peritoneum lateral to the sigmoid colon is grasped and pulled medially to expose the left peritoneal reflection, which is then opened along the white line of Toldt using cautery or scissors. The left ureter is identified at the base of the sigmoidal fossa on the medial aspect. Remaining in the correct retroperitoneal plane exposes the Gerota fascia and left ureter. Care should be taken to avoid injury to the ureter and left kidney. Depending on the need for splenic flexure mobilization, the dissection can be extended further cephalad at this moment. Mobilization of the splenic flexure is performed as described earlier in the left hemicolecctomy section.

STEP 4: VASCULAR PEDICLE LIGATION

By scoring the right and perirectal peritoneum on a cephalad direction, the origin of superior hemorrhoidal and sigmoidal vessels can be exposed. The window in the mesentery on either side of the vessels is identified and developed. After ensuring that both ureters are not in the field, the vascular pedicle at the level of superior hemorrhoidal and sigmoidal vessels can be divided at the level of aortic bifurcation or just below the takeoff of the left
colic vessels. The vascular stapler, Harmonic scalpel, or LigaSure can be used according to the preference of the surgeon.

**STEP 5: MOBILIZATION OF THE RECTUM**

During oncologic resection, care should be taken to avoid penetration of the mesorectal fascia. With the left side of the table inclined upward, the rectum is retracted anteriorly and right, and the left lateral dissection of the sigmoid is continued along the left lateral aspect of the rectum. The proximal aspect of the presacral space is exposed, which can be partially entered and developed. The operating table is now positioned with the right side inclined slightly upward. Retraction of the sigmoid colon and proximal rectum anteriorly, the right perirectal area is open and further retraction on the peritoneum allows for creating the presacral space. The presacral space is now developed with sharp dissection to the pelvic floor. Care should be taken to identify and protect the hypogastric nerves; they should be gently swept down toward the sacrum. The right presacral plane is opened to meet the left presacral plane. The rectum is then elevated anteriorly with sufficient traction that the presacral plane can be developed as far distally as needed to achieve at least 4 cm of distal mesorectal and 2 cm of distal bowel clearance below the tumor. It is generally necessary to work from the posterior section to the lateral section and anterior section and then again going deeper to all, repeating the steps until the dissection is carried well below the tumor. The anterior dissection should include the Denonvilliers’ fascia in cases of cancer. We would go above the peritoneal reflection anteriorly and take the anterior peritoneal reflection with the specimen. The lateral stalks would typically need to be divided to facilitate deep exposure of the pelvis and mobilization of the rectum for any tumors that present below the upper rectum.

Once the dissection is carried to levators, endoscopy can confirm the optimal level of rectal and mesorectal transection.

**STEP 6: EXCISION OF THE RECTUM**

The mesorectum can be divided with a LigaSure or Harmonic scalpel. A stapler is required to transect the rectum. The introduction of the stapler typically occurs through a small suprapubic incision or the hand port. The dissected rectum can be divided intracorporeally with a laparoscopic
articulating linear stapler at both of the ends. The resected specimen is then extracted out through the supraumbilical incision. Of note, it is also feasible to transect the distal rectum with a TA stapler, introduced through a small suprapubic incision that can be used later for specimen extraction (Fig. 50-22).

**FIGURE 50-22** Division of lower rectum with transverse stapler. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

**STEP 7: ANASTOMOSIS**

A purse-string suture is placed in the proximal resection margin and the anvil is tied around the margin of the colon. Then the proximal colon with the anvil is returned to the abdomen. The incision is then closed and the pneumoperitoneum is reestablished. The circular stapler is inserted through the anus, and the anvil attached to the shaft of the stapling device is advanced across the staple line under direct visualization (Fig. 50-23). The anvil of the proximal colon is attached to the stapler, approximating the bowel ends, and then the device is fired under direct visualization. The abdomen is then
irrigated with saline and hemostasis ensured. The anastomosis is checked for any leaks by filling the pelvis with saline, insufflating the rectum with air from the flexible scope, including the proximal colon with an alligator clamp, and observing for any air bubbles. If there is evidence of a leak, that area should be reinforced with sutures or diversion created. The pneumoperitoneum is vented and the port sites are closed as described previously.
Hand-Assisted Laparoscopic Low Anterior Resection

The patient is positioned in the same way as for the laparoscopic procedure. A 6- to 8-cm lower midline longitudinal incision is made to accommodate the hand port. The incision size should be a half-size smaller than the surgeon’s hand to maintain effective pneumoperitoneum. Then the surgeon’s left hand in the gel port guides the placement of other trocars. A 30-degree laparoscope is placed in the supraumbilical port and cautery attached to the scissors is placed in the RLQ port. The surgeon’s left hand provides retraction of the sigmoid colon and the rectum to aid in the dissection. The vessels are divided intracorporeally with the help of LigaSure or vascular stapler. After a clear plane is developed around the rectum, the rectum is divided with the linear TA stapler at the marked site. The rectosigmoid along with the mesorectum is extracted out through the incision made for the hand port. The coloanal anastomosis is performed using the circular stapling device in the same manner as detailed for the laparoscopic procedure above. Then the anastomotic site is checked for any leakage before closing of the abdomen.

Laparoscopic Abdominal Perineal Resection

**STEP 1: PATIENT POSITION AND ROOM SETUP**

Preoperative marking of the stoma site is essential to ensure proper stomal positioning and optimal postoperative care and function. The patient is placed in a modified lithotomy position and securely strapped. The surgeon stands on the right side of the patient initially during sigmoid and left colon dissection and later moves toward the patient’s left side for the majority of the rectal dissection. The monitor should be positioned according to the position of the surgeon. Using two monitors can alleviate having to reposition the monitor during surgeon relocation.

**STEP 2: PORT PLACEMENT AND EXPLORATION**
The use of five ports offers more flexibility in doing an APR. A 30-degree laparoscope is introduced through an infraumbilical trocar. One of the trocars is introduced at the stoma site marking, while the other three trocars are inserted in the right upper, right lower, and left lower quadrants (Fig. 50-24). Using 10-mm trocars allows the surgeon to transfer the laparoscope to other ports to get better access during the procedure. Inspection of the abdomen is carried out to confirm the pathology.
FIGURE 50-24  Position of laparoscopic ports for abdominal perineal resection (APR). (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

STEP 3: VASCULAR LIGATION
The origin of the superior hemorrhoidal and sigmoidal vessels can be
exposed by scoring the right and perirectal peritoneum in the cephalad direction. After the window in the mesentery on either side of the vessels is developed and it is ensured that both ureters are not in the field, the vascular pedicle at the level of superior hemorrhoidal and sigmoidal vessels can be divided at the level of aortic bifurcation or just below the takeoff of the left colic vessels, as described for the anterior resection.

**STEP 4: MOBILIZATION OF THE SIGMOID COLON AND THE RECTUM (ABDOMINAL PORTION)**

The mobilization of the sigmoid colon and the rectum is performed as described in low anterior resection. During oncologic resection, care should be taken to avoid penetration of the rectum or the mesorectal fascia. With the left side of the table inclined upward, the rectum is retracted anteriorly and right, and the left lateral dissection of the sigmoid along the white line of Toldt is continued along the left lateral aspect of the rectum. Then the left ureter should be identified at the base of the sigmoidal fossa. The proximal aspect of the presacral space is exposed, which can be partially entered and developed (see Fig. 50-18). The operating table is now positioned with the right side inclined slightly upward. Retraction of the sigmoid colon and proximal rectum anteriorly, the right perirectal area is open and further retraction on the peritoneum allows for creating the presacral space. The presacral space is now developed with sharp dissection to the pelvic floor. Care should be taken to identify and protect the hypogastric nerves; they should be gently swept down toward the sacrum and to identify the ureters. The rectum is then elevated anteriorly with sufficient traction that the presacral plane can be developed as far distally as needed to achieve at least 4 cm of distal mesorectal and 2 cm of distal bowel clearance below the tumor. It is generally necessary to work from the posterior section to the lateral section and anterior section and then again going deeper to all, repeating the steps until the dissection is carried well below the tumor. The anterior dissection should include the Denonvilliers’ fascia in cases of cancer. We would go above the peritoneal reflection anteriorly and take the anterior peritoneal reflection with the specimen. The lateral stalks should be divided to facilitate deep exposure of the pelvis and mobilization of the rectum for any tumors that present below the upper rectum. Then the mesorectum is divided at the chosen level with the ultrasonic scissors. The rectal dissection
is now performed anteriorly without drifting away from the mesorectal plane into the seminal vesicles and prostate or the vagina anteriorly.

**STEP 5: PERINEAL RESECTION**

The perineal dissection is performed as for conventional APR. A purse-string suture is used to close the diamond-shaped perianal incision that is created just outside the sphincter complex to include the sphincters in the specimens. The dissection of the ischial rectal fat is carried out posteriorly all the way to level of levators. Next, the anterior fat is divided in a similar fashion. Using the tip of the coccyx as a guide, a scissors is brought just anterior to the tip of the coccyx and placed into the pelvis and spread. Withdrawing the scissors in a spread position creates a common hole between the pelvis and the perineum. A finger then can be placed along the left levator and the levators divided on both the left and right sides. Hemostasis is achieved with the cautery and suture ligation as needed. The resulting defect in the pelvic floor is typically large enough that the rectum can be brought out from the abdomen and pelvis through the posterior perineal wound.

**STEP 6: EXTERIORIZATION OF THE SPECIMEN AND WOUND CLOSURE**

Anterior levators are divided on both sides along the edge of the everted rectum. Care must be taken to avoid inadvertently creating a defect in the rectum in cases of cancer. Last, the direct anterior dissection is completed, and here we would avoid any excessive use of cautery in the male in particular. The urethra is quite close to the rectal dissection and it is highly sensitive to heat. A delayed urethral leak will occur if excessive heat is applied during the anterior dissection. Finally, the rectum is extracted out through the perineal wound. The perineal wound is closed in sequential layers with absorbable sutures leaving closed-suction drains either from the abdomen down to the pelvis or, if preferred, through the perineum. The drains are clamped and pneumoperitoneum can be recreated. The descending colon is inspected to ensure that it is not twisted or rotated on its mesentery, as it is going to be used for the colostomy.

**STEP 7: COLOSTOMY**
The distal end of the colon is now brought to the colostomy orifice using a grasper. At least 3 cm of colon is extracted out through the skin and the colostomy is matured in a Brooke fashion by inverting the bowel wall so that the stoma is slightly raised above the skin.

**Hand-Assisted Laparoscopic Abdominal Perineal Resection**

The abdominal portion of the procedure is assisted using the hand port. The sigmoid colon and the rectum are mobilized as detailed previously for the low anterior resection. The perineal resection is performed as for conventional APR.

**LAPAROSCOPIC RECTOPEXY**

**Resection Rectopexy**

This procedure is essentially the same as for anterior resection with the exception being the addition of presacral fixation.

**STEP 1: PATIENT POSITION AND ROOM SETUP**

The patient is placed in the modified lithotomy position and carefully positioned and strapped on the operating table. The surgeon and the assistant stand on the right side of the patient, while the monitor is placed on the patient’s left side in the caudal end.

**STEP 2: PORT POSITION AND EXPLORATION**

A 30-degree laparoscope is introduced through the 10/12-mm subumbilical port. A careful inspection of the liver, small bowel, and the peritoneal surfaces is performed. Under direct visualization, three ports are made in right lower, right upper, and left lower quadrants.

**STEP 3: VASCULAR LIGATION**
The table is now positioned with left side and feet upward, and then the bowel loops are swept to the right side of the abdomen to make the operative field clear. The retroperitoneal structures are dissected to identify the sigmoidal and superior hemorrhoidal vessels and ureters. Because this procedure is indicated for benign cases, the vascular ligation can be performed more distally. The nerves should be spared and the ureters identified. The mesentery can be taken close to the bowel if the surgeon attempts to preserve the vascular pedicle.

**STEP 4: MOBILIZATION OF THE RECTOSIGMOID**

The sigmoid colon is mobilized by developing a plane between the mesentery and the sigmoid colon. The rectosigmoid junction is drawn toward the patient’s right side and the lateral attachments are divided. The dissection of the descending colon should be kept as minimal as possible.

**STEP 5: MOBILIZATION OF THE RECTUM**

The rectum is mobilized in a similar fashion as detailed in low anterior resection, with some modifications. To minimize chances of rectal prolapse recurrence (particularly in patients presenting with early-onset prolapse), we would dissect the rectum all the way to the levators. Although we favor transection of the lateral stalks, this should be at the discretion of the surgeon and based on factors of risk of recurrence versus risk of pelvic floor dysfunction. To not divide the rectal stalk puts the patient at a higher risk of recurrent prolapse. However, to transect both rectal stalks makes the patient at least theoretically at risk for more pelvic floor dysfunction and also removes a source of blood supply (ie, the middle hemorrhoidal). We typically preserve the superior hemorrhoidal and then transect the lateral stalks, so the rectum is supplied by inferior and superior hemorrhoidal vessels.

**STEP 6: DIVISION OF THE RECTUM AND ANASTOMOSIS**

Before the proximal or distal rectum is divided, careful measurements should be made of where the two ends of the colon and rectum match up. There should be no tension on the anastomosis once it is complete, and yet there
should be little to no laxity in the residual bowel as it lies in the pelvis. This will help reduce the risk of recurrent prolapse. Of note, some do not prefer to conduct a colon resection, and we would agree that if there is no redundancy in the colon and the patient suffers from fecal incontinence rather than from constipation, we might also choose not to resect the bowel. Once the level of colon and rectal transection has been determined to create a tension-free but nonlaxed anastomosis, the rectum is divided with a linear stapler. The division point of the rectum should be just below the level of the sacral promontory. The specimen is extracted through a small lower midline incision. In those cases where a hand port is performed, the specimen is readily extracted through the port site. The proximal end of the colon is divided, and the angle of the circular stapler is inserted and closed with a purse-string suture. The circular stapler is inserted through the anus with the trocar brought out just in front of or behind the transverse staple line. The two parts of the stapler are coupled and the device then fired. We often place a row of seromuscular sutures around the anastomosis, especially if there is any evidence of leakage when it is tested in a saline-filled pelvis.

**STEP 7: RECTOPEXY**

Once the anastomosis is complete, the mesorectum is then attached to the sacral promontory or as one of two with two or three nonabsorbable sutures. We would incorporate the lateral edge of the rectal tissue with care being taken to find the mesorectal tissue without major vessels or nerves. We would also take care to offset the left and right sutures to avoid “crimping” or occluding the rectal lumen from this fixation process. Care should also be taken to insert the needle into some of the presacral periosteum and away from the area of the sacral nerve and internal iliac vessels.

**Laparoscopic Subtotal Colectomy with Ileorectal Anastomosis**

**STEP 1: PATIENT POSITION AND ROOM SETUP**

The patient is carefully placed in a modified lithotomy position and securely strapped and padded to the operating table, thus keeping the patient stable when the operating table is tilted side to side during surgery. The surgeon
stands on the right or left side of the patient, depending on the segment of the colon. The video monitors are adjusted according to the surgeon’s position to maintain the alignment of the camera, instruments, and surgical fields. Two monitors are used for convenience because the surgeon will have to reposition at least twice. If an ileostomy is planned, the site should be identified by stomal therapists preoperatively and marked before surgery starts.

**STEP 2: PORT PLACEMENT AND EXPLORATION**

A 10/12-mm port is made in the supraumbilical region and laparoscope is introduced. Under direct visual guidance, four ports are placed, one each in all four quadrants of the abdomen. A 10-mm port is placed in the RLQ to allow the endoscopic stapler; the remaining ports are 5 mm in size. If camera position needs to be changed, a 5-mm port can be changed to a 10-mm cannula.

**STEP 3: MOBILIZATION OF THE COLON—LEFT COLON, SIGMOID COLON, AND RIGHT COLON**

The colon is mobilized sequentially starting from splenic flexure and left colon, followed by right colon and then the sigmoid colon as previously described under individual hemicolectomies. The vessels are ligated intracorporeally and simultaneously along with the dissection of its respective segment. In cases of benign pathology, the vessels can be ligated closer to the bowel and a LigaSure or other vascular transecting device can be used for most, if not all, of the vessels.

**STEP 4: EXTERIORIZATION OF THE COLON AND DIVISION OF THE VASCULATURE**

The colon is confirmed free from all attachments with the help of a grasper before exteriorization of the specimen. The pneumoperitoneum is vented and supraumbilical incision is extended for 4 to 6 cm inferiorly. The colon is exteriorized through this incision. Any remaining vascular pedicles can be ligated using standard open technique extracorporeally. The orientation of the ileal mesentery should be preserved to prevent torsion and small bowel
internal herniation.

**STEP 5: FORMATION OF ILEORECTAL ANASTOMOSIS**

An ileorectal anastomosis is performed with the help of the circular stapler in a fashion similar to that described previously for colorectal anastomosis. The tricky part of the ileorectal anastomosis is finding the optimal orientation for the small bowel and its mesentery as it comes to a lie within the pelvis. It is often difficult to get the best orientation because the ileum typically is in the RLQ, not in the LLQ. In some cases, it will easily work end-to-end for an anastomosis, but in most cases a side ileum to end of rectum may be best to achieve a mesenteric alignment to avoid seeping. If a side of ileum to end of rectum anastomosis looks best, the stapled distal end of the small bowel can be oversewn with seromuscular sutures and a separate antimesenteric site chosen to conduct the anastomosis. In this case, the anvil of the stapler can be placed in the bowel and closed with a purse-string suture and the shaft of the stapler brought across the anus into the rectum and coupled, closed, and fired in the typical fashion.

**RESTORATIVE TOTAL PROCTOCOLECTOMY WITH ILEAL J-POUCH ANAL ANASTOMOSIS**

**Laparoscopic Ileal Pouch-Anal Anastomosis**

This procedure is essentially the same as the subtotal colectomy plus ultralow anterior rectal resection. The main difference here is the creation of an ileal J-pouch rather than a colon J-pouch.

**STEP 1: PATIENT POSITION AND ROOM SETUP**

The patient is placed in modified lithotomy position and securely and safely strapped to avoid movements and injury during the procedure. The position of the surgeon should be ergonomically altered depending on the dissection of individual segment of the colon. The key to the appropriate position of the surgeon is to maintain a parallel view with the laparoscope, working instruments, and the monitors.
STEP 2: PORT PLACEMENT AND EXPLORATION

The 30-degree laparoscope is introduced through the 10-mm trocar in the infraumbilical site. The abdomen is inspected to confirm the pathology. Under direct visual guidance, four trocars are introduced in the four quadrants (Fig. 50-25). A 10-mm trocar is inserted in the right lower quadrant, while the rest of the trocars can be of 5 mm caliber. Using 10-mm trocars at all the ports will allow flexibility to the surgeon in using the laparoscope from any of the ports.
STEP 3: COLON MOBILIZATION

The colon is mobilized sequentially starting from splenic flexure and left colon, followed by right colon, and then the transverse and sigmoid colon as
previously described under individual hemicolecotomies. We prefer to mobilize the splenic flexure early while all natural attachments are intact. Intracorporeal vascular ligation and division is performed simultaneously with the dissection and mobilization of the colon using a vascular stapling device for larger vessels such as ileocolic and the LigaSure or similar device for smaller vessels.

**STEP 4: RECTAL MOBILIZATION**

The surgeon continues the dissection from the sigmoid colon toward the rectum. The rectum is fully mobilized to the pelvic floor as previously described in the section on ultralow anterior resection. The rectum is then divided at the pelvic floor using an Endo GIA (Covidien, Mansfield, MA) linear cutting stapler. If the stapler cannot reach the pelvic floor, the stapler can be introduced through a small suprapubic incision or the hand port incision, or alternatively using a transanal approach. For the transanal approach, the anal canal is exposed using a Lone Star retractor (Lone Star Medical Products, Stafford, TX) or Gelpi retractor. Diluted epinephrine solution is then injected to raise the mucosal layer to assist in mucosectomy and to minimize bleeding. Cautery dissection starts at the dentate line and is continued cephalad by lifting the mucosal layer up to the level of puborectalis, that is, the top of the anal canal. At this point, the dissection is carried full thickness to complete the distal transection of the rectum with complete mucosal removal but with preservation of the internal sphincter. This approach is used when the entire specimen can be removed through the anus.

**STEP 5: EXTERIORIZATION OF COLON AND RECTUM**

The infraumbilical incision is extended by 4 to 6 cm inferiorly after the pneumoperitoneum is vented through the cannulas. The colon is exteriorized through this incision if it has not been removed through the anus while in transanal resection. The vascular pedicles are ligated and divided using standard open technique extracorporeally unless the vessels are ligated and cut intracorporeally. The ileum at the junction with the right colon is stapled and transected.
STEP 6: FORMATION OF ILEAL J-POUCH–ANAL ANASTOMOSIS

The distal staple line of the ileum is oversewn with a seromuscular layer. Next, one makes sure that the blood supply and the vascular pedicle of the ileum are properly oriented without twists. At this juncture one needs to make sure that the apex of the pouch can reach the level of the top of the anal canal. Lengthening of the ileum to achieve the pouch–anal anastomosis must be performed before the pouch is stapled and actually created. The mesentery of the small bowel needs to be fully mobilized all the way up to the base of the stomach near the pancreas. Vascular arcades can be ligated in order to get the pouch to reach in extreme cases, and after a period of temporary bulldog clamping has been performed to ensure good blood supply. Once the pouch is thought to reach, the “J” configuration is created using two 15-cm limbs of small bowel. Seromuscular suture helps secure the correct orientation and reinforce the staple line that is to be created. At this juncture, a small enterotomy is made in the apex of the pouch, and this allows multiple firings of the 80- to 100-mm linear stapler to create the pouch itself. Once the stapling is completed (two, at most three firings), look for and correct any defects at the intersections of the staple line and check for pouch hemostasis prior to placing the handle and the purse-string in the apex.

The purse-string is made in the pouch apex, and the circular stapler is placed and suture is tightened. The pouch is returned to the abdominal cavity with proper orientation and laid in the pelvis. The midline incision is closed so that the pneumoperitoneum can be restored and the anastomosis completed. The circular stapling device is inserted through the anus and the trocar advanced under direct vision across the transverse staple line or purse-string at the anal level. The anvil of the stapler is then attached using a specially designed laparoscopic instrument ensuring that the pouch and its mesentery are lying in the correct orientation and not rotated. The stapler is coupled, closed, fired, and withdrawn. Removing the purse-strings allows us to see if the donuts are intact. Anastomotic integrity of the pouch is checked before wound closure (Fig. 50-26).
When a transanal approach is utilized to transect the distal end of the rectum, the pouch is delivered to the anal opening and two layers of absorbable sutures are placed. The first layer is seromuscular suturing of the pouch to the anal canal musculature, that is, an anchoring layer. The pouch is
then opened and four quadrant sutures are next placed between the full thickness of the pouch and the residual anal mucosal layer. Supplemental sutures complete this layer.

**STEP 7: FORMATION OF LOOP ILEOSTOMY**

The ileum proximal to the pouch by roughly 30 to 50 cm is grasped and brought out to the RLQ port. A defunctioning loop ileostomy is made, ensuring that the orientation is properly defined. Pelvic drains are placed through the laparoscopic ports. The skin is then closed and the ileostomy matured.

**Hand-Assisted Ileal J-Pouch–Anal Anastomosis**

The patient is placed in modified lithotomy position and securely strapped to the operating table. The hand port is placed in a lower midline incision. Three ports are made respectively at supraumbilicus, right lower, and left upper quadrants. The surgeon may stand on the right or left of the patient; alternatively, it is often convenient for the surgeon to stand between the legs, especially for takedown of flexures and the transverse colon. A 10-mm port is preferred to a 5-mm port as it allows the surgeon to use the laparoscope from any of the ports. The colonic mobilization commences at the splenic flexure. Additional assistance for the splenic mobilization can be provided with a grasper placed in the RLQ. After mobilizing the splenic flexure and left colon, the surgeon shifts position to mobilize the right colon and the transverse colon. Vascular ligation and division can be performed in intra- or extracorporeal manner depending on the mobilization of the colon. The rectum can be mobilized and resected at the pelvic floor with a linear stapler or with a transverse stapler as described above. The rectum and colon are then delivered through the wound and the terminal ileum divided with the linear stapler. A J-pouch is then fashioned in the same manner as described previously and anastomosed to the anus with circular stapler inserted through the anus. If a defunctioning loop ileostomy is planned, a loop of proximal ileum is passed through the RLQ port and the ileostomy matured. Care should be taken to avoid torsion of the vascular pedicle and small bowel intussusception. Drains are placed into the pelvis through the lower quadrant port. After checking for anastomotic integrity and hemostasis is done, the
hand port wound is closed in two layers as regular wound incision.

## COMPLICATIONS

Intraoperative complications including management and prevention can be seen in Tables 50-5 through 50-7. Table 50-8 shows the advantages and disadvantages with robotics.

### TABLE 50-5: INTRAOPERATIVE COMPLICATIONS

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<tbody>
<tr>
<td>Patient position related</td>
</tr>
<tr>
<td>• Lower extremity neuropathies (peroneal nerve and compartment syndrome)</td>
</tr>
<tr>
<td>• Upper extremity neuropathies (brachial plexus, median, and ulnar nerves)</td>
</tr>
<tr>
<td>Veress needle or trocar insertion related</td>
</tr>
<tr>
<td>• Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Pneumoperitoneum related</td>
</tr>
<tr>
<td>• Vessel puncture and hemorrhage</td>
</tr>
<tr>
<td>• Bowel perforation</td>
</tr>
<tr>
<td>Technique related</td>
</tr>
<tr>
<td>• Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>• Hypothermia</td>
</tr>
<tr>
<td>• Hypercarbia and acidemia</td>
</tr>
<tr>
<td>• Insufflation with misplaced needle</td>
</tr>
<tr>
<td>• Hemorrhage</td>
</tr>
<tr>
<td>• Anastomotic leakage</td>
</tr>
<tr>
<td>• Infection</td>
</tr>
</tbody>
</table>

### TABLE 50-6: MANAGEMENT OF INTRAOPERATIVE COMPLICATIONS
<table>
<thead>
<tr>
<th>Intraoperative Complications</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation</td>
<td>Laparoscopic repair, if technically feasible, or conversion to open surgery</td>
</tr>
<tr>
<td>Splenic injury</td>
<td>Control of capsular bleeding, electrocautery, topical hemostatic agent, conversion, and/or splenectomy</td>
</tr>
<tr>
<td>Ureteral injury</td>
<td>Conversion to open surgery and repair over a stent</td>
</tr>
<tr>
<td>Bladder injury</td>
<td>Laparoscopic repair, if feasible, or conversion</td>
</tr>
<tr>
<td>Mesenteric bleeding</td>
<td>Laparoscopic clip, suture control, or conversion</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>Repair and/or diversion</td>
</tr>
</tbody>
</table>

**TABLE 50-7: PREVENTION OF INTRAOPERATIVE COMPLICATIONS**
<table>
<thead>
<tr>
<th>Technique-Related Complications</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation</td>
<td>Use atraumatic instruments; exert traction on peritoneal attachments rather than on bowel; use gentle manipulation; avoid cautery injury to well-insulated laparoscopic tools and adequate visualization of tools during the application of cautery</td>
</tr>
<tr>
<td>Splenic injury</td>
<td>Ensure adequate visualization when at the splenic flexure, and place gentle traction on tissues attached to the spleen</td>
</tr>
<tr>
<td>Ureteral injury</td>
<td>Properly identify and avoid cautery in the ureter field; use ureteral stents as necessary</td>
</tr>
<tr>
<td>Bladder injury</td>
<td>Use catheter decompression</td>
</tr>
<tr>
<td>Mesenteric bleeding</td>
<td>Create mesenteric windows in avascular plane, use of double-clip technique or suture ligation for major vessels</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>Ensure proper bowel alignment, avoid tension, and check for good vascularization of proximal and distal ends, use suturing or stapling techniques, and check bleeding</td>
</tr>
<tr>
<td>Wound/trocar site infection</td>
<td>Proper antibiotic prophylaxis and ensure hemostasis and irrigation of trocar site</td>
</tr>
<tr>
<td>Trocar site recurrence</td>
<td>Protect the port site, use bag for specimen extraction, and avoid chimney effect.</td>
</tr>
</tbody>
</table>
LEARNING CURVE AND CREDENTIALING

Laparoscopic colectomy is different from other laparoscopic surgery as it requires working in multiple fields and different orientations. Proper training and experience along with appropriate help from the first assistant and the scrub nurse are vital in performing laparoscopic colectomy. There is a significant learning curve during which the length of each procedure may be longer and rate of conversion to open may be greater, although the incidence of complications is not altered. It is recommended that surgeons develop their laparoscopic skills initially with simpler procedures such as appendectomy, cholecystectomy, and right colectomy before they graduate to benign complex operations and undertake cancer resections. Based on the prerequisite of 20 laparoscopic colectomies for COST trial, ASCRS recommended that surgeons perform 20 laparoscopic resections before undertaking procedures for cancer. HALS is easily adaptable for routine and complex cases. The steep learning curve of laparoscopic-assisted colectomy can be overcome by starting with the HALS approach.

FUTURE CONSIDERATIONS—ROBOTICS AND NOTES

Successful telerobotic-assisted laparoscopic sigmoid and right colectomies were first reported by Weber et al. in 2002 when actual dissection and mobilization were performed with robotic assistance, and a lot of progress was achieved in technological inventions and its application in various operations. D’Annibale et al. reported the results of 53 robotic colorectal

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>1. 3D visualization</td>
<td>1. High initial maintenance and cost</td>
</tr>
<tr>
<td>2. Better movement of instruments</td>
<td>2. Absence of tactile sensation</td>
</tr>
<tr>
<td>3. Absence of fulcrum effect</td>
<td>3. Long setup time for instruments</td>
</tr>
<tr>
<td>4. Less fatigue</td>
<td>4. Technical experience required</td>
</tr>
</tbody>
</table>
surgeries in 2004 and concluded that the outcomes are similar to laparoscopic surgery.\textsuperscript{30} Short-term outcomes of a randomized pilot study by Baik et al. comparing robotic-assisted low anterior resection and laparoscopic low anterior resection concluded the safety and feasibility of robotics (da Vinci robots [Intuitive Surgical, Inc., Sunnyvale, CA]) in colorectal surgery.\textsuperscript{31}

Robotic-assisted surgery (da Vinci robots) offers many advantages over laparoscopic surgery such as 3D visualization, increased degrees of freedom of movement, absence of fulcrum effect, reduced fatigue, and elimination of tremor and better ergonomics for surgeon.\textsuperscript{29–31} The biggest drawback for robotics is the high cost. Minor drawbacks include the absence of tactile sensation and the lengthy time required for setup, longer operative times, as well as increased expense.\textsuperscript{32} Robotic surgery in the colorectal field has increased in popularity and is increasingly being used in pelvic surgery especially. The results of the ROLARR trial, a multinational, multicenter prospective trial comparing laparoscopic and robotic surgery for rectal cancer, will shed light on its usefulness in colorectal surgery. At this point, there is no shortage of enthusiasm in its application, especially with the new XI platform, which permits multiquadrant surgery. Most studies are retrospective, single-institution, and have mixed recommendations. Thus far it does not appear to be inferior to laparoscopic surgery, and though some studies found that conversion to open surgery is lower, a recent meta-analysis found that the conversion rate is higher.\textsuperscript{32,33}

NOSE (natural orifice specimen extraction) technique was performed in colon and rectal surgery specimen extraction through the transanal and transvaginal routes in the recent past and was considered a prequel to NOTES (natural orifice transluminal endoscopic surgery).\textsuperscript{34}

NOTES is an interesting concept that is gaining enthusiasm. It utilizes the concept of approaching the internal viscera through natural openings such as the mouth (stomach), the anus, and the vagina. NOTES was first performed in India by Reddy and Rao in a burn patient where abdominal incision was not feasible.\textsuperscript{35} Initial studies were focused mainly on animal studies.\textsuperscript{36} The Natural Orifice Surgery Consortium for Assessment for Research (NOSCAR) was formed in 2005, and it identified the potential barriers in clinical practice of NOTES and set guidelines for future research and development.\textsuperscript{37} Patients prefer to undergo the NOTES approach over laparoscopic cholecystectomy for lack of pain (99%) and external scarring (89%).\textsuperscript{38} The potential
advantages of NOTES include no scars, less pain, fewer wound complications, earlier mobility, and potential to offer therapy outside of the operating room (intensive care unit [ICU]).

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38. Varadarajulu S, Tamhane A, Drellichman ER. Patient perception of natural orifice transluminal

PERSPECTIVE ON COLORECTAL NEOPLASMS

Martin R. Weiser

ROBOTIC SURGERY

Robotic surgery builds on the innovations of laparoscopy, which has been increasingly adopted for colon and rectal cancer surgery over the past 2 decades, with numerous well-designed trials demonstrating short-term advantages in terms of recovery and complication rates, along with long-term oncologic outcomes at least equivalent to those of open surgery. These advantages likely result from the fact that laparoscopic approaches provide improved visualization of the surgical field, which translates into greater operative exposure, exploiting one of surgery’s most fundamental tenets.

As the technical challenges of laparoscopy have limited its adoption for colorectal cancer treatment, robotic systems, which resolve many of the mechanical and optical limitations of laparoscopy, are a promising technologic advance. In place of the rigid nonarticulating instruments and suboptimal visualization employed in manual minimally invasive procedures, robotic surgical equipment provides flexible instrumentation and wristed movement capabilities. Reliance on a secondary expert surgeon is reduced
due to a third robotic arm for self-assistance, and perspective is enhanced by high-definition 3-dimensional views from a mounted, stabilized, surgeon-controlled camera.\textsuperscript{1,2} The superior ergonomics and surgical dexterity provided by the robot result from the instruments’ 7 degrees of freedom and 90-degree articulation, permitting manipulation within small spaces, a capability particularly relevant in the narrow, bony pelvis.\textsuperscript{3,4}

Compared to laparoscopy, robotic technology has been shown to enhance dexterity by 65%, reduce skill-based errors by 93%, and shorten the time needed to complete a task by 40%.\textsuperscript{5} Robotic technology also provides motion scaling and tremor filtering, facilitating precise dissection and suturing, which is particularly valuable in dissecting along the origins of the mesenteric vessels during complete mesocolic excision or in performing total mesorectal excision (TME) within the pelvis.\textsuperscript{6} In addition, the robotic platform enables an integrated and supervised teaching environment without compromising operative or long-term outcomes.\textsuperscript{4}

There are no absolute contraindications to robotic colon and rectal cancer surgery, and its application is limited primarily by the surgeon’s experience and expertise. Relative contraindications, depending on the surgeon’s judgment, are locally invasive tumors and recurrent disease, which often obscure normal anatomic planes. In addition, consideration should be given to whether a patient can tolerate pneumoperitoneum and steep positioning.

Another advantage of robotic systems is that they simplify complex surgical maneuvers such as intracorporeal suturing and creation of intracorporeal anastomoses. Creation of the bowel anastomosis intracorporeally after colon resection may cause less visceral trauma and tissue stretching and might therefore contribute to faster recovery of bowel function and, consequently, reduced length of hospital stay.\textsuperscript{7-9} In addition, after completion of an intracorporeal anastomosis, the specimen can be removed through a smaller or alternate site, which may reduce the risk of surgical site infections and incisional hernias.\textsuperscript{4,10}

The Robotic Versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial was the first multicenter, prospective, randomized controlled trial examining robotic surgery versus conventional laparoscopic surgery for the curative treatment of rectal cancer.\textsuperscript{11} The trial was conducted from 2011 to 2014 and involved 40 surgeons from 29 sites in 10 countries, with 51.4% of the patients randomized by surgeons recruiting >20 patients. The median
numbers of procedures previously performed by each surgeon were 91 laparoscopic TMEs and 50 robotic TMEs. Of the total 471 patients, 237 were randomized to robotic resection and 234 were randomized to laparoscopic resection, with 466 patients ultimately undergoing surgery.

The conversion rate to open surgery (overall 10.1%) was 12.2% in the laparoscopic arm compared to 8.1% in the robotic arm (adjusted odds ratio [OR], 0.61; \( P = .16 \)). In multilevel logistic regression, significantly greater odds of conversion were noted in obese patients (adjusted OR, 4.69; \( P < .001 \)) and in men compared to women (adjusted OR, 2.44; \( P = .04 \)). Operating surgeon experience had a mild-to-moderate effect on the odds of conversion based on the intracluster correlation coefficient estimate of 0.05, suggesting that most participating surgeons were experts in conventional laparoscopic surgery but still learning robotic surgery. The authors concluded that laparoscopic experience has a negligible influence on surgeons’ gains in robotic skills over time. Surgeons who had completed approximately 28 robotic procedures had the same odds of conversion as laparoscopic surgeons with triple the case volume experience (91 cases), suggesting that fewer robotic cases are needed to achieve reliable results than are required to reach expert level in laparoscopy.

Secondary oncologic end points included circumferential resection margin (CRM) positivity (5.1% for robotic surgeries vs 6.2% in the laparoscopic arm) and odds of achieving the highest standard plane of surgery (mesorectal plane; no significant difference). Compared to the COLOR II, CLASICC, ALaCaRT, and ACOSOG Z6051 trials, however, the ROLARR trial had the lowest rates of CRM positivity. No significant difference was reported in 30-day complication rates (33.1% in robotic arm vs 31.7% in laparoscopic arm), including the anastomotic leak rate (12.2% in robotic arm vs 9.9% in laparoscopic arm), or in postoperative bladder and sexual function.

**ROBOTIC RIGHT COLECTOMY TECHNIQUE**

The patient is placed supine on the operating table. The arms are secured by the patient’s side, pressure points are protected with padding, and the patient is confirmed to be secure on the table. A Veress needle inserted below the left subcostal margin in the midclavicular line is the preferred method of establishing pneumoperitoneum because it allows rapid access and is
appropriate for all patients. For extracorporeal anastomosis, an 8-mm robotic trocar is placed superior to the umbilicus. Three additional robotic 8-mm ports are placed: left upper quadrant, midline subumbilical, and right lower quadrant. An assistant port for pneumoperitoneum or AirSeal device is placed in the left lateral position (Fig. 51-1). The patient is then placed in a slight Trendelenburg position, with an 8- to 12-degree left-sided downward tilt. The peritoneal cavity is inspected for metastatic disease to confirm the feasibility of resection, and the omentum is then displaced cephalad to allow retraction of the small bowel into the left abdomen. The robotic cart is positioned on the same side as the pathology. The 0-degree robotic camera is inserted into the supraumbilical port, a monopolar scissor is inserted in the left upper quadrant port, a bipolar fenestrated grasper is inserted in the infraumbilical port, and a Cadiere is inserted in the right lower quadrant port.
We routinely perform medial-to-lateral dissection, beginning along the superior mesenteric vein to locate the origin of the ileocolic pedicles, consistent with the principles of complete mesocolic excision. In the right lower quadrant, arm 4 provides lateral and anterior traction to the cecum and terminal ileum to generate tension for lifting the ileocolic vessels. The retroperitoneum is incised along the path of the superior mesenteric vein, and all nodal tissue is cleared with the specimen. The ileocolic pedicle is identified, the retroperitoneal space immediately below the vessels is entered, and a retromesenteric dissection is developed. The duodenum and the head of the pancreas are displaced posteriorly, and the ileocolic artery and vein are ligated and divided using the vessel sealer at their origins (Fig. 51-2). The dissection continues cephalad along the superior mesenteric artery and vein to expose the middle colic vessels and gastrocolic trunk using an infracolic approach. The improved visualization, articulating instruments, and retraction of the robotic platform are particularly useful for ensuring dissection of all nodal disease at the base of the middle colic pedicle (for hepatic flexure or transverse colon lesions) or right branch of the middle colic pedicle (for cecal and ascending colon lesions) (Fig. 51-3).
FIGURE 51-3 Division of the middle colic artery using a vessel sealer.

Dissection then continues both laterally and cephalad over the Gerota fascia toward the lateral congenital parietal attachments and underside of the hepatic flexure. The hepatic flexure is next addressed; the assistant retracts the transverse colon caudally using the right lower quadrant and subumbilical arms, and the surgeon dissects using the left upper quadrant arm (Fig. 51-4). The gastrocolic ligament is separated from the transverse colon, beginning at the falciform ligament, entering into the lesser sac, continuing proximally toward the hepatic flexure, and separating the omentum off the superior border of the proximal and mid transverse colon to facilitate later exteriorization.
For extracorporeal anastomosis, the mid and distal transverse colon should be mobilized to ensure sufficient laxity to allow exteriorization of the bowel. The mesentery of the terminal ileum is released from the retroperitoneum, and the congenital peritoneal attachments are incised while holding the inferior pole of the cecum and appendix, continuing dissection up the right paracolic gutter to complete the medialization of the right colon. The terminal ileal mesentery should be fully mobilized to the duodenum to ensure a tension-free anastomosis, often facilitated by increasing Trendelenburg positioning. The robot is undocked after a grasper has been placed on the ileocecal junction. The umbilical incision is lengthened to accommodate a wound retractor, and the colon is then delivered through the wound. The resection and anastomosis are completed in the usual fashion, and the colon is then returned into the abdomen.\textsuperscript{12,13}

Intracorporeal anastomosis is especially preferred for patients with a high body mass index, shortened transverse colon mesentery, and transverse colon lesions, since transverse colon mobilization is not required and the specimen can be removed via a Pfannenstiel incision. The stapler is generally introduced via a mid-left lateral port, and the anastomosis is created isoperistaltically with suture closure of the common enterotomy/colotomy (Fig. 51-5).
FIGURE 51-5 Intracorporeal isoperistaltic anastomosis between the terminal ileum and transverse colon.

ROBOTIC RECTAL TOTAL MESORECTAL EXCISION TECHNIQUE

Rectal resections can be divided into 2 major stages: (1) an abdominal stage, which involves mobilization of the left colon and splenic flexure and division of both the inferior mesenteric artery (IMA) and the inferior mesenteric vein (IMV) and (2) a pelvic stage, during which rectal dissection and TME are performed.

Dissection during the abdominal stage can be accomplished in a number of ways, including medial-to-lateral, lateral-to-medial, and IMV first. A medial-to-lateral approach allows easy visualization and control of the mesenteric vasculature early in the procedure, immediate delineation of the plane between the mesentery and the retroperitoneum, preservation of the autonomic nerves, early identification of the left ureter and other retroperitoneal structures, and quick access to the splenic flexure.

Certain steps in the robotic TME procedure described herein require particular attention to avoid complications. High ligation of the IMA and division of the IMV near the ligament of Treitz facilitate colonic
mobilization. Failure to complete these steps reduces the likelihood of properly connecting the colon to the lower rectum or proximal anal canal and increases the risk of constructing an anastomosis under tension. Vascular division should be performed after the left ureter is clearly identified, as this structure travels lateral to and in very close proximity to the IMA. Avoiding damage to autonomic nerves requires special attention in the following anatomic areas: (1) the superior hypogastric plexus during dissection of the IMA; (2) the hypogastric nerves at the sacral promontory during entry into the retrorectal space; (3) the pelvic plexus during lateral mobilization of the rectum; and (4) below the peritoneal reflection during anterior dissection of the rectum.

The patient is placed in the modified lithotomy position, with the buttocks slightly over the end of the table. The thighs are abducted and aligned with the contralateral shoulder. The hips, particularly on the left side, should be fully extended, and the knees should be flexed at 45 degrees so that the legs are not in the way when the robot is docked at the left hip. Both legs should be gently rotated internally to avoid lateral pressure on the peroneal nerve. The patient’s arms are placed alongside the body to lessen the possibility of shoulder injury and to provide sufficient space for the surgeon and assistant as well as the robotic platform. Pressure points and bony prominences are padded, and the body is secured to the operating table. Before proceeding, the patient’s secure positioning is confirmed by testing the table in the Trendelenburg position and in a left-sided tilt.

After insufflation via Veress needle placed below the left costal margin in the midclavicular line, the camera port is placed just above the umbilicus, and 8-mm ports are placed in the right upper quadrant, right lower quadrant, and left mid abdomen. A 12-mm trocar is placed roughly halfway between the umbilicus and right anterior superior iliac spine, which corresponds to the midclavicular line, and often can be used as an aperture for a diverting loop ileostomy. An accessory port is also placed lateral in the right mid abdomen (Fig. 51-6).
FIGURE 51-6 Port placement for robotic low anterior resection. For pedicle ligation and splenic flexure, mobilization ports 1a, 2, and 3 are used. For pelvic dissection, ports 1b, 2, and 3 are used.

For pedicle ligation and splenic flexure mobilization, the right-side ports are used (see Fig. 51-6), with the patient in a slight Trendelenburg position with a 12- to 15-degree tilt. The small bowel is swept laterally, and the omentum is placed over the liver, exposing the IMA and IMV. A bipolar fenestrated grasper is used in the left upper quadrant port, the monopolar scissor is used in the left lower abdominal port, and the Cadiere grasper is used in the lowest left quadrant port. With the Cadiere holding tension on the sigmoid mesentery, the peritoneum at the sacral promontory is incised, the autonomic nerve is swept into the retroperitoneum, and the IMA is identified. In a medial-to-lateral dissection, the sigmoid mesentery is dissected off the retroperitoneum in an avascular plane. After identification of the gonadal
vessels laterally, the ureter medially, and the IMV at the ligament of Treitz and just inferior to the pancreas *(Fig. 51-7)*, the left colon is mobilized off the retroperitoneum medially to laterally in an avascular plane. The IMV is divided using the vessel sealer via the left midabdominal port.

**FIGURE 51-7** Dissection of the inferior mesenteric vein adjacent to ligament of Treitz and inferior to pancreas.

The splenic flexure is then mobilized by further elevating the left colon mesentery off the retroperitoneum and then off the pancreas with entry into the lesser sac. Next, the omentum is dissected off the distal transverse colon, and the left colon lateral wall attachments are divided along with the remaining retroperitoneal attachments of the splenic flexure of the colon *(Fig. 51-8)*.
After the IMV is divided and the left colon is mobilized, the IMA should take on the characteristic T-shaped structure, branching into the cranial left colic artery and caudal superior hemorrhoidal artery (Fig. 51-9). The position of the ureter and gonadal vessels in the retroperitoneal plane is reconfirmed, and the IMA is ligated and divided using the same implement as for the IMV. Because the left ureter travels just lateral to the IMA, the dissection must be adequate to avoid injuring it when attempting to divide the IMA. The medial-to-lateral dissection continues toward the abdominal wall using a blunt dissection to gain entry into the previously developed avascular plane beneath the IMV and advance toward the sacral promontory. As the gonadal vessels and the ureter are encountered, they should be dissected posteriorly toward the retroperitoneum. Visualization of the psoas muscle usually indicates that the dissection is too deep and in the wrong plane.
Following division of both the IMA and the IMV, the lateral attachments of the sigmoid and descending colon are divided. These include the line of Toldt, which is divided using monopolar cautery. This dissection, starting at the left lower quadrant, is facilitated by retracting the colon medially and anteriorly. Division of the line of Toldt reveals the medial dissection plane; as dissection progresses toward the left upper quadrant, any omental attachments to the colon should be divided, leaving attachments between the omentum and the abdominal wall in place, unless visualization is impaired.

The entire left colon should now be medialized and mobilized so that attention can be directed at the proposed site of mesenteric ligation and colon transection for future anastomoses. The mesentery of the descending colon is then divided from the stump of the IMA toward the colon to the point of the future division of the bowel, usually at the junction of the descending and sigmoid colon. The mesentery should be divided using an energy source or several firings of a vascular stapler. Dividing the marginal artery at this time avoids tearing vessels during extraction.

After colonic mobilization, pelvic dissection can begin. The robotic arms are detached from the trocars, and the patient is leveled and placed in a
significant Trendelenburg position to keep the small intestines out of the pelvis. The robotic system should be redocked at the patient’s left hip, permitting access to the anus and perineum (see Fig. 51-6). As the assistant elevates the rectosigmoid junction (or grasps the divided mesenteric pedicle of the superior rectal artery), dissection begins posteriorly at the sacral promontory, entering the avascular plane between the visceral and parietal layers of the endopelvic fascia.¹⁴

At the beginning of dissection, the hypogastric nerves should remain in the retroperitoneum (Fig. 51-10). As dissection continues distally, the surgeon must keep in mind that the rectum curves upward and anteriorly as the anorectal junction is approached. Just above the levator ani muscles, the endopelvic fascia fuses with the mesorectal fascia. To avoid bleeding and injury to the fascia, the dissection uses monopolar cautery and smooth maneuvers, and the mesorectum is manipulated using a gauze tie rather than robotic graspers. The TME proceeds along the areolar plane down to the rectococcygeal ligament.

FIGURE 51-10 Posterior mesorectal excision and right lateral dissection.

Anteriorly, the peritoneal reflection is incised, and the dissection is continued along the rectovaginal septum in women or over the rectovesical or rectal prostatic fascia (Denonvilliers fascia) in men (Fig. 51-11). Arm 3 is used to retract the bladder and other anterior structures as dissection proceeds
The articulation of the robotic scissor tips enables the surgeon to perform the dissection using ideal approach angles: as distally as possible in the posterior plane, which facilitates identification of the lateral stalks and dissection in the anterolateral areas. In most cases, the surgeon alternates between the posterior, lateral, and anterior planes to achieve complete circumferential dissection.

**FIGURE 51-11** After the peritoneal plane is incised, dissection should continue along the rectovaginal septum in women or rectovesical fascia in men.

Laterally, dissection proceeds along the sidewalls medial to both ureters, contouring along the curving mesorectal plane. Injury to the autonomic plexus and generation of excess medial traction on the sidewall, which jeopardize transection of the nervi erigentes, should be avoided. As the lateral stalks are divided, care should be taken to preserve the hypogastric plexus and the pelvic sidewall, lateral to the seminal vesicles in men and the cardinal ligaments in women. The lateral stalks are controlled with bipolar cautery or monopolar cautery using the scissors and divided.

Anteriorly, the peritoneum between the rectum and seminal vesicles or upper vagina is dissected under direct vision by simultaneous retraction of the anterior structures toward the pubis, and the rectum toward the sacrum. During this dissection, the planes are less distinct, and the fat on the anterior
mesorectum can be thin, so the anterior pelvic structures are elevated off the anterior rectal wall. The dissection continues through Denonvilliers fascia, which is separated from the anterior structures and kept with the specimen. The distal point of this dissection matches that of bowel transection, which depends on the level of the tumor. Middle and distal rectal tumors require removal of the entire mesorectum, while an upper rectal tumor requires transection of the rectum and mesorectum 5 cm below the level of the tumor.\textsuperscript{15}

Dissection continues down to the pelvic floor, separating the fatty mesorectum from the levator muscle. The rectum is lifted off the muscle and cleared circumferentially for transection. This mobilization of the rectum increases the distance of the tumor from the dentate line, allowing an adequate distal margin and preservation of the sphincters. Continuing dissection further down allows the surgeon to access the intersphincteric plane if necessary for ultralow anterior resection with intersphincteric dissection. In preparation for rectal division, the rectum is examined digitally and by flexible endoscopy to ascertain the level of the tumor. Using the 12-mm trocar port, a 45-mm robotic stapler is used to divide the rectum, after which the robotic cart can be undocked. We routinely extract the specimen through a 3- to 4-cm supraumbilical right lower quadrant (site of future diverting ileostomy) or suprapubic Pfannenstiel incision covered with a wound protector. The proximal bowel is divided, and an anvil is secured to the proximal colon with a purse-string suture. The descending colon conduit is returned to the peritoneal cavity, and the wound protector is twisted to occlude the wound so that pneumoperitoneum can be reestablished. The circular stapler is introduced through the anus, and an end-to-end anastomosis is constructed under robotic vision (Figs 51-12 and 51-13).
FIGURE 51-12  After rectal stapling, the circular stapler is passed per anus to the stapled end of the rectum.

FIGURE 51-13  End-to-end intracorporeal stapled anastomosis between the descending colon and the rectal stump, with complete exposition of the pelvic space. The uterus can be retracted using a stitch.
CONCLUSION

Robotic surgery was developed to overcome the limitations of conventional laparoscopy and to help surgeons perform complex procedures. This technique has demonstrated a range of advantages that could change the way we approach colorectal cancer.

ACKNOWLEDGMENTS

We thank Rosa M. Jimenez-Rodriguez, MD, and Jessica Moore, MS.

REFERENCES


RECTUM AND ANUS
Benign diseases of the anorectum range from relatively simple disorders such as hemorrhoids and fissures to extremely complex problems associated with pelvic floor abnormalities.

ANATOMY

The rectum normally lies attached to its mesorectum within the curve of the sacrum, with limited mobility. The junction of the rectosigmoid is usually fixed by the inferior mesenteric artery and peritoneal attachments. The rectum and mesorectum (fat and vessels) follow the curve of the sacrum to the pelvic floor. The rectum exits the pelvis behind the prostate or vagina through a slit in the pelvic floor. The horseshoe-shaped puborectalis muscle
circles from its origin on the pubis around behind the rectum and reinserts on the pubis anteriorly. Contraction of the muscle pulls the rectum forward, creating a more acute angle at the palpable anal-rectal ring. The anal canal is a 3- to 4-cm long funnel-shaped extension of the pelvic floor voluntary musculature called the external sphincter. The pressure generated by contracting this circular muscle prevents egress of rectal contents. The internal sphincter muscle is a thickened continuation of the circular muscle of the rectal wall. As such, it is an autonomic muscle and has no voluntary control. It is innervated by a local plexus of nerves that connects the stretch receptors of the rectal wall to the internal anal sphincter as a sampling reflex (anal inhibitory reflex) which produces relaxation as the rectum fills.

The anorectum receives both sympathetic and parasympathetic nerves. The sympathetic nerves originate from thoracolumbar segments and unite below the inferior mesenteric artery to form the inferior mesenteric plexus. Injury to these nerves results in retrograde ejaculation and infertility in men. These fibers then descend to the superior hypogastric plexus located on the sacral promontory just inferior to the aortic bifurcation. These purely sympathetic fibers bifurcate and descend as the hypogastric nerves. Parasympathetic fibers from S2, S3, and S4 (the nervi erigentes) join the hypogastric nerves in the side wall of the low pelvis, anterolateral to the rectum, to form the inferior hypogastric plexuses. Mixed fibers from the plexuses innervate the prostate, rectum, bladder, penis, and internal anal sphincter. These autonomic plexuses of the pelvic nerves run around the lateral aspect of the pelvic rim to enter the prostate and seminal vesicles anteriorly. The sympathetic innervation of the internal sphincter is motor, while the parasympathetic innervation is inhibitory. Injury to the pelvic autonomic nerves during pelvic surgery may result in urinary retention or erectile dysfunction.

The innervation of the voluntary muscles of the pelvic floor is via direct fibers from S2, S3, and S4 in the pelvis from the sacrum (Fig. 52-1). The motor and sensory nerves of the external sphincter are derived from S2, S3, and S4 nerve roots from the sacral plexus and they arrive at the external sphincter via the pudendal nerve around the ischial spine at Alcock’s canal. The vagina is closely approximated to the anterior surface of the rectum and anal canal and separated from the rectum by the embryologic potential space known as Denonvilliers’ fascia. Dissection posterior to Denonvilliers’ fascia in a male protects the nervi erigentes on the posterior surface of the prostate.
from injury and preserves erectile function.

![Diagram of the pudendal nerve.](image)

**FIGURE 52-1** Diagram of the pudendal nerve. Note the five regions in which it runs and the three divisions into which it divides. (Reproduced with permission from Anderson JE: *Grant’s Atlas of Anatomy*, 8th ed. Baltimore, MD: Williams & Wilkins; 1983.)

It is useful to consider the anus and surrounding structures as a single unit: the anorectum (Fig. 52-2). The anorectum includes the perianal skin, the anal canal, the anal sphincters, and the distal rectum. The three main anatomic points of reference are the anal verge, the dentate line, and the anorectal ring. The distal external boundary of the surgical anal canal is the anal verge, which is the palpable intersphincteric groove between the lowest fibers of the internal and external sphincter. At this point the anal epithelium (anoderm) is devoid of hair follicles, sebaceous glands, and apocrine glands that are present in the perianal skin.
The cephalad border of the anatomic anal canal is a mucocutaneous junction, the dentate line, and a zone of transitional cuboidal cells. This union of the embryonic ectoderm with the endodermal gut resides approximately 1.0 to 1.5 cm above the anal verge. The anal transitional zone (ATZ) is 6 to 12 mm in length and the columnar epithelium of the rectum changes to cuboidal epithelium that joins the squamous epithelium at the dentate line.

The upper border of the surgical anal sphincteric complex is the anorectal ring. It may be palpated by digital examination about 1.0 to 1.5 cm above the dentate line. The anatomic anal canal begins at the dentate line and ends at the anal verge. The surgical anal canal starts at the anorectal ring and terminates at the anal verge. This latter definition of the anal canal is used throughout this chapter.

Just above the dentate line, the rectal mucosa forms 8 to 14 longitudinal folds known as the rectal columns. Between each two columns at the dentate line is a small pocket termed an anal crypt. Small, rudimentary secretory anal glands open into some, but not all, of these anal crypts. The ducts of the glands extend through the internal sphincter as far as the intersphincteric plane, where the glandular tissue resides.

Below the dentate line, cutaneous sensations of heat, cold, touch, and pain are conveyed by afferent fibers in the inferior rectal nerves. Cephalad to the dentate line, visceral sensitivity to vibration or when the mucosa is pinched, such as when internal hemorrhoids are ligated, are carried by parasympathetic fibers. These fibers participate in the sampling reflex in the continence complex.

The superior rectal artery, the terminal branch of the inferior mesenteric artery, descends to the upper rectum where it divides into lateral branches. Subsequent smaller divisions penetrate the rectal wall. The middle rectal arteries arise from the internal iliac arteries and supply the distal rectum and upper anal canal. The inferior rectal arteries, branches from the internal pudendal arteries, cross the ischiorectal fossae to supply the anal sphincters and the distal rectum (Fig. 52-3). The collateralization between these three sources provides the rectum with an impressive resistance to ischemia.
FIGURE 52-3  Vascular supply of the anus and rectum. Blood returns from
the anus via two routes. Below the dentate line, the external hemorrhoidal plexus drains into the inferior vena cava via inferior pudendal veins. Above the dentate line, the internal hemorrhoidal plexus drains into the portal system via the superior rectal vein.

There are two paths for venous blood return from the anorectum. Above the dentate line, venous blood flows into the portal system through the superior rectal vein and inferior mesenteric vein. Below the dentate line, the external hemorrhoidal plexus drains into the internal iliac vein via the middle rectal vein or via the pudendal vein, which receives blood from the inferior rectal vein. This can become a source of venous collateralization when portal vein flow is compromised.

**FECAL INCONTINENCE**

**Pathophysiology**

Injury to the anal sphincter complex and the resulting anal incontinence is usually due to obstetric injury, trauma, or fistula disease in which the external muscle is divided or damaged (Table 52-1). Neurogenic incontinence is due to stretching of the pudendal nerves during prolonged labor, chronic descent of the perineum and nerve stretch during straining at stool or rectal prolapse, or systemic disease such as multiple sclerosis, scleroderma, or spinal cord injury. Idiopathic incontinence is due to medical disease such as diarrhea in a patient with limited rectal capacity, irritable bowel syndrome, or sedatives that cause poor sensation in the anal canal in patients with no evidence of neurogenic or mechanical incontinence. The subject of anal incontinence is covered in Chapter 53.
The rectum normally holds between 200 and 250 mL. It distends readily with filling and has limited muscular activity intrinsically. The internal anal sphincter provides 80% of the resting anal sphincter pressure that provides the resistance to gas and mucus at the anal canal. The sampling reflex is a function of rectal distension causing internal anal sphincter relaxation via an intramural reflex to the internal sphincter. The rectal contents can then be sensed in the sensory nerve–rich transitional zone and anoderm to discriminate the true nature of the rectal contents. This sampling reflex occurs frequently throughout the day to provide continence and also serves to initiate the defecation process. The voluntary external sphincter muscle contraction in response to this sampling reflex provides the final active component of fecal continence. The subconscious voluntary contraction of the external sphincter, puborectalis, and pelvic floor muscles provide complete control of rectal contents. The pelvic floor muscles maintain continual activity, even during sleep, to provide fecal continence. This also seems to be a learned response because infants and children require 1 to 2 years to achieve control.

RECTAL PROLAPSE AND INTERNAL INTUSSUSCESSION

Pathophysiology

The true etiology of rectal prolapse and intussusception is unknown. The mechanism is influenced by three components: (1) The rectum and
Rectosigmoid junction have increased mobility off the sacrum; (2) descent of the rectosigmoid junction into the pelvis allows a funnel-shaped intussusception into the rectum as the rectum attempts to expel itself; and (3) poor relaxation of the pelvic floor and external sphincter mechanism occurs during straining (Fig. 52-4). Persistent straining against this outlet obstruction may lead to descent of the perineum, expulsion of the rectum, and true rectal prolapse. This sequence of events from progression of internal intussusception (funnel formation) to full rectal prolapse is supported anecdotally. Consequences of rectal prolapse include anal canal injury from stretch of the internal sphincter during rectal prolapse and/or injury to the pudendal nerve during descent of the perineum. The classic defecographic picture of rectal prolapse and severe intussusception is a funnel that descends into the deep pelvis as the rectosigmoid junction descends. A ball valve obstruction occurs at the level of the anal canal before it is pushed through to the outside.

FIGURE 52-4 Rectum with internal intussusception. (Reproduced with permission
A distal mucosal prolapse is occasionally mistaken for full rectal prolapse. The typical appearance of a mucosal prolapse is that of mucosa separated by radial lines around the anus (Fig. 52-5A). Concentric rings of mucosa are seen in true rectal prolapse (Fig. 52-5B). Defecography is helpful to distinguish between these two entities.
Diagnosis and Evaluation

Signs and symptoms of rectal prolapse include rectal pressure and pain, incomplete evacuation, outlet obstruction, and constipation causing prolonged straining. Mucus discharge and bleeding from the fully prolapsed tissue may also be present. Examination most often reveals concentric rings of rectal tissue with a patulous anal canal, poor voluntary tone, and a very mobile rectum within the vault. Proctosigmoidoscopy reveals descent of tissue during straining and occasionally an ulcer on the anterior wall (caused by ischemia at the lead point of the intussusception). Defecography reveals extreme mobility of the rectum from its point of fixation to the sacrum, redundancy of the mesorectum, and funnel formation as the rectum prepares to descend through the anal canal opening at the pelvic floor. Defecography is most useful in cases that cannot be visualized in an office setting. Thickened barium simulates stool and cinedefecography allows visualization of the defecating process; this is particularly helpful in cases in which mucosal prolapse is suspected and the intent is to rule out full rectal prolapse. Four-contrast cinedefecography (rectum, vagina, and small bowel and bladder as needed) also helps delineate complex pelvic floor abnormalities. This technique is gradually being replaced, or at least supplemented, by dynamic MRI of the pelvic floor.

A grading system of intussusception has been developed to assist in planning management (Table 52-2). Mild to moderate intussusception with some mobility, some funnel formation, and descent of the rectum can usually be treated conservatively with biofeedback for poor relaxation of the pelvic floor and high doses of bulk fiber to fill the rectum and limit intussusception. However, grade 4 intussusception with severe outlet obstruction may require operative resection of the redundant rectum or rectopexy to secure the rectum to the sacrum.\textsuperscript{1} The most appropriate setting for operative treatment of internal intussusception is the patient who has developed moderate incontinence from the intussusception and straining or the patient who has severe bleeding from the solitary rectal ulcer at the tip of the funnel.
Anal manometry can be useful to document the preoperative function of the sphincter if there is not an obvious patulous anal canal on examination. Electromyography can provide objective evidence of pudendal nerve injury (pudendal nerve terminal motor latency [PNTML] >2.0 msec/cm) and allow some prediction of continued recovery after repair.

Management

Rectal Prolapse. Numerous techniques exist for management of rectal prolapse; over 100 procedures have been described. The four basic types of procedure include rectopexy, low anterior resection, perineal proctectomy, and anal encirclement.\(^2\)

The low anterior resection technique uses the standard technique for removal of the middle and upper portions of the rectum and redundant sigmoid colon. The left colon is reattached to the upper or middle third of the rectum by using either a double-staple or hand-sewn technique (Fig. 52-6). The rectum is mobilized to the level of the pelvic floor circumferentially, but preserving the anterolateral ligaments carrying the middle rectal arteries and splanchnic nerves. The left colon and rectum (now in continuity) are returned...
to the curve of the sacrum and the peritoneal flaps sutured to the sacrum to keep the rectum on stretch. The incidence of fecal incontinence may be higher after this procedure because the rectal capacitance is reduced. Postoperative evacuation difficulties may be noted if the nerves within the anterolateral ligaments have been divided. Preoperative anal physiological testing may assist in the selection of patients who are candidates for low anterior resection (ie, no evidence of sphincter injury or dysfunction).
FIGURE 52-6  Laparoscopic low anterior resection with colorectal anastomosis—double-staple technique. A. Laparoscopic positioning of the patient and surgeon. The patient is secured to the table in modified lithotomy
position. The operating surgeon stands to the right of the patient. Trocar placement is based on use of hand-assisting devices and surgeon preference. 

**B.** Lateral approach to mobilization of the sigmoid colon and identification of the left ureter. 

**C.** Laparoscopic mobilization and dissection of the rectum down to the lateral ligaments. 

**D.** Intracorporeal colorectal anastomosis: a descending colon purse-string suture is tied around the shaft of the anvil. This can also be performed extracorporeally with a hand-assisting device or via a small incision. 

**E.** Completed anastomosis with stapler still in place.

Suture rectopexy, accomplished by mobilizing the rectum posteriorly to the pelvic floor and placing sutures to the sacrum through the redundant peritoneal attachments to fix the rectum in a straight line to the pelvic floor, results in low recurrence rates in well-selected patients. Laparoscopic suture rectopexy is the method of choice in most hospitals and is associated with fewer complications and a shorter hospital stay. The technique of anterior Prolene mesh rectopexy, described by D’Hoore, mobilizes the anterior rectum to the anal canal and suspends the rectum with mesh attached to the sacral promontory. Sutures attach the mesh to the anterior rectum at the level of the rectovaginal septum. The redundant cul-de-sac is excised and the peritoneum is closed over the mesh along its path on the right side of the rectum to the sacral promontory. Results suggest rapid recovery, good control of prolapse, reduction of constipation, and limited morbidity.

A perineal proctectomy with anterior and posterior reefing of the sphincter muscle to restore the pelvic floor opening to its original size can be used in the elderly patient with full rectal prolapse and incontinence. The entire prolapsing rectum and redundant sigmoid are removed through a perineal approach beginning at the top of the transitional zone columns (Fig. 52-7). The left colon or proximal sigmoid is sutured to the transitional zone 1 to 2 cm above the dentate line. The external anal sphincter and pelvic floor muscles can be reefed in the anterior and posterior midline to restore anal tone in patients with incontinence, as described by Prasad et al. The incidence of recurrent prolapse is approximately 10% in patients with good sphincter function. It actually carries a higher risk of complication than laparoscopic rectopexy and has slowly been replaced, even in the highest risk elderly patients, by the laparoscopic or robotic approach. This procedure is not technically possible in patients who have mucosal prolapse alone or patients with high rectal prolapse and an intact anal canal and normal
sphincter.

**FIGURE 52-7** Perineal proctectomy. A. Patient in the prone jackknife
position. After gentle traction is applied on the rectal wall, a diluted epinephrine solution is injected into the outer layer of the prolapsed rectal wall. B. A circular incision is made through the full thickness of the outer layer of the prolapsed segment just proximal to the everted dentate line. C. The rectal prolapse has been completely unfolded. The mesenteric vessels are carefully ligated close to the bowel wall. D. The rectum is elevated anteriorly to expose the presacral space. A posterior rectopexy is performed (arrow) by approximating the seromuscular layers of the bowel wall to the presacral fascia above the levator anu muscles. E. The levator anu muscles are approximated posteriorly (arrow). This repair pushes the bowel anteriorly to help recreate the anorectal angle. F. One or two sutures are used to approximate the levators anterior to the rectum to reinforce the pelvic floor. G. The prolapse is amputated and the colon sutured to the dentate line in a circumferential fashion (dotted line). H. Completed anastomosis. (Reproduced with permission from Prasad ML, Pearl RK, Abcarian H, et al: Perineal proctectomy, posterior rectopexy, and postanal levator repair for the treatment of rectal prolapse, Dis Colon Rectum 1986;Sep;29(9):547-552.)

Anal encirclement procedures have been mostly replaced by the perineal proctectomy. The anal encirclement procedure using synthetic material such as nylon mesh should be limited to the extremely debilitated patient or the elderly patient who cannot withstand perineal proctectomy. It can be effectively performed under local anesthesia in patients with prohibitive surgical risks and decreased life expectancy. A rolled silastic mesh may be adequate to reinforce the sphincter orifice with minimal postoperative recovery period. The risk of erosion increases in the patient with a large amount of scar tissue in the perineum.

**Internal Intussusception of the Rectum**

The treatment of internal intussusception of the rectum is primarily conservative with use of a high-fiber diet. High doses of psyllium may prevent formation of the funnel and eliminate the associated outlet obstruction with normalization of bowel function. Patients with pelvic floor outlet obstruction (nonrelaxation of the puborectalis) may benefit from biofeedback. In patients without pelvic floor outlet obstruction and with severe symptoms from the intussusception (ie, bleeding or incontinence), an operation may be considered. A low anterior resection or rectopexy is
appropriate for these patients depending on whether they have constipation or incontinence, respectively. The treatment of a bleeding solitary rectal ulcer by low anterior resection usually requires an ultralow anterior resection and coloanal anastomosis in the setting of an extremely thickened anterior rectal wall that overwhelms even the thickest staple height. Perineal proctectomy is not recommended because the sphincter mechanism is intact and resection of redundant rectum will be extremely difficult in patients with an incomplete prolapse. Colonic transit times are helpful to document normal colonic transit. Defecography will identify the level of the funnel formation within the rectum and mobility of the rectum away from the sacrum. A balloon expulsion test can document or rule out pelvic floor outlet obstruction as a cause of the intussusception.

The use of transanal stapling (STARR [(stapled transanal rectal resection)] or Transtar) procedures has become popular in Europe. Patient selection is important, as those with other abnormalities such as enteroceles, larger rectoceles, or nonrelaxation of the puborectalis were found not to have good response after the STARR procedure. Complications include bleeding, perineal pain, recurrence, or incontinence. In a trial comparing STARR versus biofeedback, the STARR procedure was found to be more effective in improving symptoms of obstructed defecation. It may be performed in unhealthy individuals under local anesthetic by a properly trained individual after failure of biofeedback.

PELVIC FLOOR OUTLET OBSTRUCTION AND SOLITARY RECTAL ULCER SYNDROME

Pathophysiology

The presenting complaints of patients with pelvic floor outlet obstruction usually include some form of constipation and straining. Defecation is a learned process and pelvic floor outlet obstruction may be either a change in the defecating mechanism or a failure to learn the appropriate series of events to allow normal function. The muscle of the pelvic floor is completely normal, but the function and control are abnormal. There may be a psychologic influence in this syndrome because patients who have been
sexually abused or who have been psychologically traumatized may develop this outlet obstruction. The need to dominate and control has also been documented in these patients. The syndrome results from obstruction of the anal canal due to anterior displacement of the puborectalis muscle and contraction of the pelvic floor and external sphincter during straining to defecate. Attempts to defecate against a closed pelvic floor result in chronic funnel formation of the rectum and descent of the anterior rectal wall into the anal canal. This chronic trauma and ischemia may lead to the formation of an ulcer on the anterior wall of the rectum. The stimulus to defecate is often neglected. The end result is an uncoordinated effort at defecation with pelvic floor obstruction of the outlet, even as the rectum begins to distend and the autonomic muscles begin to relax.

It is possible that pelvic floor outlet obstruction is etiologically related to rectal prolapse and intussusception. However, no long-term studies have provided conclusive evidence. Patients may also present with megarectum from outlet obstruction, fecal incontinence due to nerve injury from chronic straining, or severe mucosal prolapse or hemorrhoids.

The solitary rectal ulcer is assumed to be due to ischemia of an isolated portion of the mucosa on the anterior rectal wall, approximately 10 cm above the anal verge, which prolapses partially into the anal canal and becomes ischemic during prolonged straining. The healing process may occasionally incorporate functioning mucosal glands beneath the new mucosal surface and form a localized area of colitis cystica profunda. These entrapped glands continue to produce mucus and are occasionally mistaken for an early neoplasm of the rectum. An increase in collagen deposition is also present and helps distinguish this from a neoplasm.

**Diagnosis and Evaluation**

Patients with pelvic floor outlet obstruction may complain of a number of problems that include constipation and straining at defecation, the need for digital maneuvers to evacuate the rectum, bleeding, mucosal prolapse, and hemorrhoids. They occasionally present with chronic pain of the anal canal and symptoms of severe spasm of the anal canal and pelvic floor. In the past this was classified as anismus, proctalgia fugax, or levator ani syndrome. Digital rectal examination may reveal paradoxical motion (tightening instead of relaxing) of the puborectalis muscle during attempts to push the finger out
of the rectum. Defecography generally shows a persistent puborectalis impression on the posterior rectum as the patient attempts to evacuate the rectal contents. Defecography tends to overdiagnose the problem of nonrelaxing puborectalis. This may be due to an unnatural setting in a cold radiology suite or possible patient embarrassment. The presence of nonrelaxing puborectalis muscle must therefore be confirmed using some other technique. The method best suited to our practice has been to have the patient expel a 60-mL air-filled soft latex balloon while sitting in a private bathroom. This simple technique of expulsion of the balloon within the confines of a private bathroom seems to be adequate. Surface electromyography (EMG) is also useful in the diagnosis and treatment of nonrelaxing puborectalis muscle, as it documents decreased pelvic floor electrical activity during proper relaxation of the muscle and an increase during paradoxical contraction. Colonic transit study will demonstrate accumulation of all of the administered radiopaque markers within the rectum after an elapsed period adequate for clearance (>7 days). An algorithm used to deal with pelvic floor disorders is shown in Figure 52-8.
Treatment and Management

The initial steps in the treatment of outlet obstruction problems include high doses of fiber and establishment of a normal bowel routine. Outpatient biofeedback using surface EMG, balloon expulsion, sensation techniques, and a simulated stool are also effective in severe cases of nonrelaxing puborectalis muscle. Psychological counseling and relaxation techniques may be helpful in patients who have a psychological component to their problem.

RECTOCELE, ENTEROCELE, AND COMPLEX
PELVIC FLOOR ABNORMALITIES

Outpouching or bulging of the rectum into the vagina (rectocele) can be seen on defecography in patients with pelvic floor disorders. These findings, however, can also be found in patients without any pelvic or bowel complaints. Surgical repair does not always lead to resolution of symptoms. No predictors of successful outcome of surgery are universally accepted from various studies examining characteristics on defecography and symptomatology. Surgical technique is the surgeon’s preference and can be performed via a transanal, transvaginal, or perineal approach to bolster, pleat, and reconstruct the muscle in the rectovaginal septum. Fortunately, the majority of patients improve with medical management.\textsuperscript{15,16} Rectoceles occurring in patients with rectal prolapse generally resolve after repair of the prolapse as long as the rectum is mobilized all along the rectovaginal septum.

An enterocele is the bulging of small bowel into the rectogenital area during cough or even constantly, causing symptoms of urinary urgency, pain, constipation, and fullness. It is usually part of a complex of pelvic floor defects. This is a common finding in patients who are status post hysterectomy, in patients with symptoms of obstructive defecation, or in asymptomatic patients. A defecography defines the problem. An enterocele can be repaired transabdominally in conjunction with operative management of other pelvic floor abnormalities by reefing or excising and reclosing the redundant pelvic peritoneum to prevent herniation of small bowel into the pelvic floor.

Pelvic floor disorders may also involve bladder or gynecological complaints. A multidisciplinary team approach for evaluation, discussion, recommendation, and operative management of complex pelvic floor abnormalities provides the best care for these patients. A urogynecologist or urologist with experience in bladder or vaginal suspension, a colorectal surgeon with experience in treatment of incontinence and rectopexy/resection, and pelvic floor suspension as well as physical therapists, psychologists, radiologists, and endoscopists define the “pelvic floor” team. Dynamic MRI is a useful modality for the diagnosis of some of these challenging pelvic floor cases.\textsuperscript{17} High-resolution 3D endovaginal and endorectal ultrasonographies are increasingly being used for evaluation of pelvic floor disorders.\textsuperscript{18,19}
HEMORRHOIDS

Current theories about the development of hemorrhoids consider the nature of anal “cushions.” These cushions are aggregations of blood vessels (arterioles, venules, and arteriolar-venular communications), smooth muscle, and elastic connective tissue in the submucosa that normally reside in the left lateral, right posterolateral, and right anterolateral anal canal. Smaller discrete secondary cushions may reside between the main cushions. Hemorrhoids are likely the result of a sliding downward of these anal cushions. Hemorrhoids provide tissue to close the anal canal during rest. It appears that the disintegration of the anchoring and supporting connective tissue and the terminal fibers of the longitudinal muscle above the hemorrhoids allows these structures to slide distally. Chronic straining and repeated thrombosis, or disruption of the vascular complex, result in tissue expansion of the cushions, stretched and redundant overlying mucosa, and visible columns of hemorrhoids.

Classification

Anal skin tags are discrete folds of skin located at the anal verge. These may be the end result of resolved thrombosed external hemorrhoids or, more rarely, may be associated with inflammatory bowel disease. Internal hemorrhoids reside above the dentate line and are covered by transitional and columnar epithelium (Fig. 52-9). First-degree internal hemorrhoids are not large and are often barely visible but result in painless bleeding during strained defecation. Second-degree hemorrhoids are large enough to protrude through the anal canal at the time of defecation and may bleed, but spontaneously reduce. Third-degree internal hemorrhoids protrude and bleed with defecation, but are large enough and stretched enough that they must be manually reduced. Fourth-degree internal or mixed hemorrhoids are a fusion of internal and external hemorrhoids as the vascular complexes and cushions descend in the submucosa and become permanently fixed below the dentate line and cannot be manually reduced.
Types of hemorrhoids

- External hemorrhoid
- Internal hemorrhoid
- Mixed hemorrhoid

Origin below dentate line (external plexus)
Origin above dentate line (internal plexus)
Origin above and below dentate line (internal and external plexus)
External hemorrhoids consist of the dilated vascular plexus located below the dentate line and are covered by squamous epithelium. They become symptomatic when the venous plexus becomes thrombosed. This clot may erode and cause pain and bleeding or resolve and leave behind a “tag” of excess skin over the anal verge. External hemorrhoids do not always follow the typical pattern that internal hemorrhoids do and may occur randomly around the anal orifice.

**Evaluation of Internal Hemorrhoids**

Even though internal hemorrhoids are the most common source of rectal bleeding, it is imperative that other causes be excluded. Because internal hemorrhoids cannot be detected by digital examination, diagnosis can only be made by anoscopy. It is mandatory that colonoscopy be performed in high-risk patients to exclude other sources of bleeding, such as carcinoma or proctitis (eg, for patients aged >40 years and those with a personal or family history of colorectal neoplasia or a change in bowel habits).

**Treatment**

Regulation of diet and avoidance of prolonged straining at the time of defecation comprise the initial treatment of mild symptoms of bleeding and protrusion. Increasing the fiber content of the diet to at least 25 to 35 g daily with raw vegetables, fruits, whole-grain cereals, and hydrophilic bulk-forming agents can reduce and often alleviate all symptoms. Symptomatic relief is provided by a daily dose of 12 g of psyllium powder in a glass of water by producing adequate bowel fiber and function for most patients complaining of constipation and hemorrhoids. If bleeding and protrusion persist, however, the hemorrhoids should be treated surgically.

Elastic ligation of the friable redundant hemorrhoidal tissue is quite satisfactory for first-, second-, and third-degree hemorrhoids. The procedure is quite simple. The hemorrhoid is visualized with the aid of an anoscope and grasped with forceps. The redundant tissue is pulled into a double-sleeved cylinder on which there are two latex bands. The bands are discharged from the cylinder, and the hemorrhoidal bundle is ligated (Fig. 52-10).
Certain precautions, however, must be taken with this form of treatment. The ligatures must be placed at least 2 to 3 cm above the dentate line on minimally innervated tissue to avoid extreme discomfort. Ideally, the ligatures should be placed at the top of the hemorrhoidal cushion. About 25% of patients experience mild, dull anorectal discomfort lasting for 2 to 3 days following the procedure. Mild analgesics and warm baths are usually sufficient to relieve the discomfort. In fewer than 1% of patients, brisk bleeding may occur when the necrotic tissue sloughs off at 7 to 10 days. Occasionally this requires suture ligation. Less than 2% of patients treated with ligation of the internal hemorrhoid develop thrombosis of an external hemorrhoid, which may cause considerable discomfort. Necrotizing pelvic or perineal sepsis is the most severe complication of ligation. Fortunately, it is rare and almost always associated with immune compromise. It requires immediate recognition in the setting of increased pain, fever, or urinary dysfunction. Treatment consists of immediate examination under anesthesia for debridement of all necrotic tissue, intravenous broad spectrum antibiotics.
covering anaerobes, and observation in the intensive care unit. Patients with poorly functioning neutrophils or reduced numbers of white blood cells for any reason (human immunodeficiency virus [HIV] patients with low CD4 count, patients on chemotherapy, brittle diabetics, patients with leukemia) should be treated with another method of hemorrhoid ablation which does not leave necrotic tissue behind, or at least be warned of and observed for the occurrence of this potentially life-threatening complication.

Hemorrhoidal elastic band ligation is an office procedure, and no special preparation is required. Patients with a bleeding diathesis or with portal hypertension are not good candidates for ligation. Usually only one hemorrhoid is ligated on the first treatment visit to prevent urinary retention, constipation, or severe spasm. Ligations can be performed every 2 to 4 weeks until all symptoms of bleeding or prolapse are alleviated. The second ligation can be multiple if the first treatment is well tolerated. Other minimally invasive procedures such as infrared coagulation and diathermy coagulation cause thrombosis of the internal vascular pedicle and stop bleeding, and may fix the loose tissue within the anal canal. They are primarily indicated for first- and second-degree hemorrhoids and may require multiple treatments. Ultrasound- or Doppler-guided ligation of hemorrhoids has received increased interest because of claims of less pain and ease of the procedure. The technique is based on the use of an ultrasound source to identify the vascular pedicle in the wall of the rectum at the apex of the hemorrhoidal cushion to suture ligate the vessel and pexy the redundant mucosa up to the lower rectal wall.

Although diet, bowel regulation, or elastic ligation will alleviate most symptoms of internal hemorrhoids, occasionally further surgical treatment may be needed. Excisional hemorrhoidectomy is indicated for large, mixed (combined internal/external) hemorrhoids that are not amenable to ligation because the ligature would have to incorporate pain-sensitive tissue at or below the dentate line.

Circular stapled hemorrhoidectomy is a technique occasionally or rarely indicated for the elective treatment of circumferential third- and fourth-degree hemorrhoids (sometimes referred to as distal mucosal prolapse) that are not permanently prolapsed due to scar. This involves placing a purse-string suture incorporating the mucosa of the upper anal canal (not the muscle of the rectal wall) circumferentially at 4 to 5 cm above the dentate line. A stapled circumferential mucosectomy and anopexy is then accomplished with
a 33-mm circular stapler incorporating all of the redundant mucosa of the distal rectum to have a circular staple line at a level 4 to 5 cm above the dentate line. This can be performed under regional anesthesia with minimal morbidity in experienced hands. Potential complications include bleeding if the staple line is incomplete, pain if the staple line is too close to the dentate line, rectovaginal fistula if the purse string captures the rectovaginal septum, complete closure of the rectum if the stapler and purse string are malpositioned, return of symptoms if the purse string is incomplete, and a syndrome of unrelenting pain in some patients if the staples persist in the wall of the rectum. Many colorectal surgeons have abandoned this technique, the author included.

THROMBOSED, PROLAPSED, INCARCERATED INTERNAL HEMORRHOIDS

Occasionally, the internal hemorrhoidal tissue may become thrombosed and incarcerated outside the anal canal, resulting in spasm of the anal sphincter, massive local edema, and severe pain. In such circumstances, the edematous tissue may be injected with a local anesthetic containing epinephrine. Dissipation of the edema by manual compression then can be achieved, allowing reduction of the prolapsed tissue into the rectum. Observation and use of stool softeners with tub soaks usually allow the acute episode to resolve without an operation because the hemorrhoidal vessels have been naturally thrombosed. The thrombosed internal hemorrhoids will sclerose and may not require surgery. If symptoms persist or recur, a three-quadrant excisional hemorrhoidectomy may then be necessary.

THROMBOSED, PROLAPSED, INCARCERATED, STRANGULATED, NECROTIC INTERNAL HEMORRHOIDS

In the circumstance where necrotic tissue is present due to strangulation of tissue at the time of acute thrombosis and incarceration of internal hemorrhoids, emergent excisional hemorrhoidectomy is necessary. Care should be taken to preserve the anoderm. The usual three-quadrant pattern is most often found and normal skin bridges will persist. The patient should be kept in the hospital after the procedure until the pain is minimal and until
spontaneous voiding is possible, and to ensure resolution of any potential infection. Prophylactic broad spectrum antibiotic coverage is recommended in patients with diabetes or immune compromise.

**MIXED HEMORRHOIDS**

The mucosal component of mixed hemorrhoids occasionally can be treated by elastic ligation above the dentate line to reduce mucus discharge and nuisance tissue prolapse. Large symptomatic, nonreducing mixed hemorrhoids generally are treated by excisional hemorrhoidectomy.

**Hemorrhoidectomy Technique**

The patient is placed in the prone flexed position with padded rolls under the hips. Local anesthesia with sedation under anesthesia monitoring using a perianal field block with 0.25% bupivacaine with or without epinephrine is usually adequate. If the patient has a history of obstructive sleep apnea, general anesthesia with control of the airway is more appropriate. The apex of the vascular pedicle is ligated first, 4 to 5 cm above the dentate line, with a 2-0 or 3-0 absorbable, soft suture. Long lasting sutures with rigidity will irritate the anal canal. An elliptical incision with cautery or sealing device starting below the apical hemostatic suture should incorporate the internal and external hemorrhoid out onto the perianal skin. The hemorrhoidal tissue is sharply dissected from the underlying internal sphincter without removing any muscle (**Fig. 52-11**). Hemostasis must be meticulous prior to closing the defect. The entire wound is then closed by running the apex suture to the distal perianal skin edge. A running locking suture guarantees hemostasis of the mucosal edges. The largest hemorrhoid is excised first, with care taken not to excise excessive tissue. If the anoderm bridges are inadequate after complete excision, a stricture is likely to form in the future. If there is any concern of leaving an adequate anal aperture covered by normal anoderm, it is best to modify a planned three-quadrant hemorrhoidectomy and instead perform a two-quadrant hemorrhoidectomy and band the remaining internal component.
THROMBOSED EXTERNAL HEMORRHHOIDS

The external venous plexus is located at the anal verge and encircles the anal canal. A segmental thrombus is confined to the anoderm and perianal skin and does not extend above the dentate line. A thrombosed external vein presents as a painful perianal mass. The overlying skin may be stretched to 2 cm or more. Pain usually peaks within 48 hours and generally becomes minimal after the fourth day. If untreated, the thrombus is absorbed within a few weeks. The pressure of the underlying clot will occasionally cause the adjacent skin to become necrotic, and the clot will be extruded through the area of necrosis. This is noted by the patient as rectal bleeding followed by relief of the anal pain. A partially extruded clot can be removed in the office to provide relief.

Treatment of thrombosed hemorrhoids is aimed at relief of the pain. If symptoms are minimal, mild analgesics, sitz baths, proper anal hygiene, and
bulk-producing agents will suffice. However, if necrosis is extensive, excision of the thrombosed hemorrhoid is usually indicated. Numerous vessels are usually involved. It is necessary to excise the entire necrotic mass along with the overlying skin and subcutaneous tissue. The wound is left open without packing. Postoperative care consists of mild analgesics and warm sitz baths or showers and bulk agents to remove the need for straining at defecation.

**ANAL FISSURE**

An anal fissure is a split in the anoderm over the hypertrophied band of internal sphincter at the anal verge (Fig. 52-12). The fissure is almost always located close to the midline of the anal canal; in men, 95% are near the posterior midline and 5% near the anterior midline, whereas in women, about 80% will be located posteriorly and 20% anteriorly. The unusual event of anterior and posterior anal fissure occurs in less than 5% of patients. The precise cause of an anal fissure has yet to be determined. Increased resting pressure in the internal sphincter must contribute. However, fissures probably are related to tearing of the anoderm at the time of defecation. Anal sphincter hypertonicity and an increase in ultraslow waves on anal manometry characterize typical anal fissures. The increased anal canal pressure that accompanies an anal fissure is associated with ischemia in the area of the fissure and prevents healing, as spasm recurs with each bowel movement. An anal ulcer is the chronic form of an anal fissure with heaped-up edges, sentinel skin tag, and often associated with an internal hypertrophied anal papilla and external sentinel skin tag.
FIGURE 52-12 Anal fissure.
Clinical Features and Diagnosis

Most acute fissures are superficial and heal rapidly with no specific treatment. Occasionally, the fissure may extend deeply through the anoderm to expose the fibers of the internal sphincter. Surprisingly, secondary infection rarely occurs.

Fissures that are aberrantly located should alert the surgeon to other causes besides hypertrophied anal sphincter. Individuals with chronic diarrhea may develop anal stenosis associated with a fissure. Anal Crohn’s disease is associated with anal fissures, which may be a primary manifestation of the disease. These fissures are associated with the edematous, painless anal skin tags typical of anal Crohn’s disease and occur anywhere around the circumference of the anus. These fissures, ulcers, and tags are often accompanied by simultaneous abscesses and fistulas. Isolated anal Crohn’s disease occurs in only 2% of patients with Crohn’s disease but will eventually occur in some form in over 80% of patients with Crohn’s disease.

Patients with anal fissures usually complain of anal pain accompanying and following defecation. Bright red bleeding may accompany a bowel movement, although it is usually minimal. A slight discharge also may be present. It is common for patients to complain of continued spasm for several hours after defecation. This spasm may move down the posterior thigh in severe cases.

An anal fissure is detected by gently separating the buttocks to reveal the lower edge of the fissure at the anal verge, where a sentinel tag also may be seen. A soft touch of a cotton swab to this area will elicit the pain and help with the diagnosis. A deep gluteal cleft or tight spasm of the sphincter may sometimes obscure the fissure, and if the patient can tolerate it, examination with a small anoscope may be required. The fissure/ulcer complex rarely extends above the dentate line. It is also possible for an anal ulcer to develop a posterior subcutaneous abscess and fistula as bacteria accumulate under the outer overhanging lip of the ulcer.

Treatment

Dietary recommendations and prescription of bulking agents to promote soft stools are beneficial, and warm tub soaks may provide sphincter relaxation
and comfort. The majority of acute fissures will heal with conservative management. The use of 0.2% nifedipine ointment applied to the anoderm of the anal verge relaxes the sphincter and dilates local vessels to promote healing. Most acute fissures will heal with this added therapy.\textsuperscript{23}

The injection of 20 to 25 units of botulinum A toxin into the internal anal sphincter at both edges of an anal ulcer and directly into the internal sphincter muscle at the ulcer base (total of 75-100 units) is a simple procedure that has been shown to heal anal fissures.\textsuperscript{24} It can be done with local anesthesia as an outpatient procedure, with symptomatic relief by approximately 1 week. The paralysis of the internal sphincter reverses in several months and the fissure may recur. Repeat treatments can be performed if the initial response was adequate, but it is expensive with at best modest complete healing rates. This has been an excellent means of treating difficult-to-heal anal ulcers in a woman who fears incontinence of gas and liquid that may occur after an internal sphincterotomy.

Surgical treatment may be required for deep, chronic fissures associated with a sentinel skin tag, hypertrophied anal papilla, and exposed internal sphincter. Excellent results can be achieved if the internal sphincter is divided laterally rather than in the midline. Furthermore, lateral sphincterotomy is not associated with a “keyhole” deformity. Only the thickened band of the internal sphincter should be divided (ie, partial sphincterotomy). This limits the amount of internal sphincter transection and reduces the potential for fecal incontinence. The sphincter band palpable under the ulcer is the only muscle that needs to be divided and the cut in the sphincter should not be longer than the length of the ulcer.

\section*{Open and Closed Sphincterotomy}

Sphincterotomy can be performed under local anesthesia, using either an open or closed technique (Fig. 52-13). The open technique consists of a radial incision of the anoderm at the right lateral position over the intersphincteric groove and limited division of the internal sphincter only up to the proximal extent of the fissure under direct vision. The thickened band of autonomic muscle is delivered into the incision over the tip of a curved clamp and divided with electrocautery to reduce bleeding. The incision is left open and the patient is started on warm tub soaks to close secondarily in a few days to
avoid infection.
Closed technique:

Blade inserted in intersphincteric groove and passed cephalad in intersphincteric plane to level of dentate line.

Blade then moved medially, dividing inferior 1/3 to 1/2 of internal sphincter.

Intact anoderm.

Internal sphincter divided; external sphincter, anoderm, and longitudinal muscle remain intact.

Open technique:

Skin incision made external to anal verge.

Hypertrophied band of internal sphincter freed and elevated into incision.

Internal sphincter divided; wound usually left open for drainage.
The closed method entails dividing the internal sphincter by a subcutaneous approach. With a Hill-Ferguson retractor in the anal canal, the tip of a #11 blade scalpel is inserted into the right lateral intersphincteric groove and turned toward the lumen of the anus. The gentle sawing motion toward the fingertip in the anus cuts the muscle fibers in a controlled way to avoid injury to the mucosa. Both techniques may be used in the outpatient setting and afford rapid pain relief. Approximately 98% of fissures heal following sphincterotomy. However, there is a small incidence of fecal incontinence following the procedure, so careful patient selection is mandatory. There is a risk of anal fistula if the tip of the scalpel breaks the mucosal surface of the anal canal during a closed sphincterotomy. The open sphincterotomy can also become infected and act like a perianal abscess.

Elderly female patients, with decreased anorectal sensation, are generally not ideal candidates for internal sphincterotomy because of the risk for anal incontinence. Consideration should be given to a diamond skin advancement flap to cover the ulcer bed in women to prevent incontinence. This flap requires isolation of a postage stamp–sized island of skin based on a subcutaneous fat pedicle from the inner aspect of the buttock posteriorly or the perineum anteriorly. The ulcer is excised leaving a defect in the size of the flap. The flap is advanced to the open area in the anoderm and secured to the freshly cut mucosal edges (Figs 52-14 and 52-15).
FIGURE 52-14  Excision of mucosal ulcer and flap design.  A. Right anal canal ectropion with stricture.  B. Excision of ectropion or ulcer.  C. House shaped skin and fat flap inscribed with scalpel.  (Reproduced with permission from Caplin DA, Kodner IJ: Repair of anal stricture and mucosal ectropion by simple flap procedures,  
FIGURE 52-15 Flap mobilization.  

A. Skin and fat “V” flap is moved into the anal canal supported by the pedicle of fat.  

B. Flap is sutured in place and donor site closed behind it to create a “Y” closure. (Reproduced with permission from Caplin DA, Kodner IJ: Repair of anal stricture and mucosal ectropion by simple flap procedures, Dis Colon Rectum 1986 Feb;29(2):92-94.)

ANORECTAL ABSCESS AND ANAL FISTULA

Diagnosis and Classification

More than 95% of all anorectal abscesses are caused by infections arising in the anal glands that communicate with the anal crypts (cryptoglandular disease). The acute phase of cryptoglandular disease is an anorectal abscess, while the chronic stage is recognized as an anal fistula. The anal glands lie in the intersphincteric space between the internal and external anal sphincters at the level of the dentate line. Obstruction of an anal duct leads to the formation of a glandular abscess in the intersphincteric plane. The clinical presentation, natural history, and proper treatment of anorectal abscess and fistula are understood easily if it is recognized that the disease originates as an intersphincteric abscess.

As the abscess enlarges, it escapes the confines of the intersphincteric plane and spreads in one of several possible directions (Fig. 52-16). The most
common of all anorectal abscesses is a perianal abscess, which presents as a tender, erythematous bulge at the anal verge. An ischiorectal abscess is formed when a growing intersphincteric abscess penetrates the skeletal muscle of the external sphincter below the level of the puborectalis and expands into the fat of the ischiorectal fossa. These abscesses can become quite large, because the levator ani (the upper border of the ischiorectal fossa) serves as the upper extent of the ischiorectal fossa and the fat of the ischiorectal fossa, which encircles the anal sphincter, offers no resistance to expansion of the abscess. An ischiorectal abscess may be palpated as a bulge above the puborectalis, although it actually lies below the levator ani musculature. In contrast to the perianal abscess, this abscess seldom presents as a visible bulge because of the large potential space in the ischiorectal fossa. Patients complain of pain of the inner buttock or low pelvis as the pressure of the abscess increases. Rarely, an intersphincteric abscess may expand upward between the circular internal sphincter and the external sphincter, forming a supralevator abscess.
FIGURE 52-16 Anorectal abscess and fistula-in-ano cryptoglandular origin theory.
Treatment

Perianal abscesses should be drained immediately, before wide fluctuance or cellulitis develops. Antibiotics are not indicated and should be used only in the presence of extensive cellulitis, valvular heart disease, diabetes, or compromised immunity. If the diagnosis is suspected but not readily evident, examination under anesthesia should be performed. This is facilitated by lighted Hill-Ferguson retractors and curved grooved probes to identify internal openings and determine potential fistula formation already present at the time of abscess drainage.

With adequate regional or general anesthesia, the abscess can be detected and localized by digital examination. An intersphincteric abscess is treated definitively by performing an internal sphincterotomy over the length of the abscess cavity, which serves to unroof and drain the abscess into the low rectum and anal canal. However, if the infection has developed into a perianal or an ischiorectal abscess, adequate drainage of the abscess cavity first must be done by making a cruciate incision or removing a disc of the skin overlying the abscess as close to the anal canal as possible. Complete evacuation of the contents of the abscess cavity is essential. In 30% of patients, the internal opening of the abscess will be obviously draining purulent material. In these cases it is appropriate to place a soft silicone seton through the drainage incision on the skin, along the tract to the internal opening, and then around the entire sphincter complex and overlying skin to be tied in a loose circle with a silk suture. The silicone seton allows the fistula tract to mature and a definitive procedure to be planned as the next step.

Incision and drainage alone will result in complete resolution of the infection in about half of patients. An anal fistula occurs in 50% of patients. A fistula is a fibrous, tubular tract with an internal opening located in a crypt at the level of the dentate line and an external opening located at the drainage site of the earlier abscess. The fistula may travel through varying amounts of muscle or fat, depending on the characteristic of the causative abscess or the drainage method applied to the abscess. It is important to allow the fistula tract to become mature, and a soft seton can be placed when the fistula is discovered. The seton is usually left in place for 4 to 8 weeks.

The appropriate treatment for an anal fistula is dependent on the anatomy and the location of the fistula tract. Goodsall’s rule states that if the anus is bisected by a line in the frontal plane, an external opening anterior to the line
(within 2 cm of the anal verge) will connect to an internal opening by a short, direct fistula tract (Fig. 52-17). However, if the external opening is located posterior to this imaginary line or anteriorly but outside 2 cm from the anal verge, the fistula tract follows a curved course to the crypt in the posterior midline. This rule, while useful, is not infallible.

![Figure 52-17](image)

**FIGURE 52-17** Surgical management of fistula-in-ano.

Occasionally, an external opening located more than 2 cm from the anal verge anterior to the imaginary bisecting line connects to an internal opening in the posterior midline. This is based on the lack of barriers to forward spread for an abscess in the ischiorectal fossa. Because of its shape, this fistula is usually called a *horseshoe fistula*. Horseshoe fistulas usually have an internal opening in the posterior midline of the anus and may extend anteriorly and laterally to both ischiorectal spaces by way of the deep postanal space. The posterior opening must be incised into the postanal space to deal with the primary cause. The anterior extensions of the horseshoe tracts then can be drained by a secondary opening, avoiding a long skin incision that would unroof the entire tract (Fig. 52-18). This is the Hanley procedure.
for a horseshoe abscess/fistula.
Horseshoe fistula with external openings anterior to midanl line and internal opening in posterior midline

Anterior extensions curetted and drained via Penrose drains through secondary incisions along tracts, avoiding along incision

Main posterior tract identified with probe

Short posterior portion of tract unroofed and involved crypt excised

Opened posterior tract

Secondary incisions

Posterior tract marsupialized

Drains
If a perianal abscess develops into a fistula that involves a small portion of the internal and very few of the most superficial fibers of the external sphincter muscle, the condition can be treated by simple fistulotomy. This “superficial fistulotomy” divides a portion of the internal sphincter and no meaningful fibers of the external sphincter to unroof the tract.

The fistula that forms after drainage of an ischiorectal fossa abscess is a transsphincteric fistula, which crosses the lower portion of the external sphincter. The fistulotomy required to unroof this tract results in division of a significant portion of the internal sphincter and external sphincter. Only a fistula in the posterior midline can be treated without worry of incontinence. However, the puborectalis must not be divided, or incontinence will invariably ensue. During posterior midline fistulotomy, a finger on the puborectalis muscle will keep the surgeon from this mistake.

The external anal sphincter is much less prominent in the anterior half of the anal canal. Thus, fistulotomy as a treatment for an anterior quadrant anal fistula is associated with an increased risk of anal incontinence, particularly in women. Consequently, treatment of such fistulas often involves eradicating the internal opening of the fistula at the level of the dentate line by advancing a flap of rectal mucosa. It is important to ensure adequate drainage of the fistula through the external opening until the suture line of the advancement flap is well healed; otherwise, an abscess can reform and disrupt the suture line (Fig. 52-19). Injection of Fibrin glue and insertion of collagen plugs into the fistula tract are alternatives with minimal morbidity and mixed success.26,27
Ligation of the intersphincteric fistula tract (LIFT) may be used with minimal morbidity and mixed success.\textsuperscript{28,29}

Through a radial incision in the intersphincteric groove the fistula can be encircled and divided with double-suture ligation. Healing has been reported for greater than 50% of fistulas treated this way. Minimal damage to the sphincter mechanism and anal canal allows other treatments to be used if the technique fails. The LIFT procedure can also be supplemented with a “postage stamp” piece of biologic mesh to separate the ends of the fistula in the intersphincteric groove. Even if the fistula recurs, the internal sphincter is the only muscle involved in the subsequent fistulotomy to finally cure the fistula.\textsuperscript{30}

The patient with a fistula that defies identification, the tract that does not follow the usual path, or the fistula that has been through multiple failed attempts at treatment are candidates for MRI of the pelvis with dilute hydrogen peroxide injected through either the internal or external opening. A 3D ultrasound may provide similar information. Other substances such as dilute povidone iodine, dilute milk, or methylene blue can be used for tracking the fistula through the pelvic tissue. The usual cause for a persistent fistula is an undrained abscess in an area of the sphincter complex which prevents access and maintains a low-grade state of purulence. Rarely extreme measures are required to generate healing, such as proximal diversion and incision and unroofing of the external component of the tract to identify the hidden abscess.

Rectovaginal (RV) fistulas after obstetric injury are best treated with a sliding advancement flap.\textsuperscript{31,32} It is important to perform preoperative testing to evaluate for an associated external sphincter defect that may need to be repaired at the time of the advancement flap. If the patient has a history of pelvic malignancy, a biopsy of the fistula tissue is important to rule out cancer as a cause. Transperineal and transvaginal approaches to repair of the RV fistula do not manage the high pressure (rectal) side of the fistula. The advancement flap repair of a high RV fistula requires creation of a full thickness rectal wall flap that has a good blood supply and no tension. The flap should be twice as wide as it is long and the tip of the flap must travel at least 2 cm to reach the distal aspect of the excised fistula. Counterdrainage of the RV septum is helpful to avoid a hematoma of the septum and disruption of the flap. It is helpful to have the patient undergo a bowel preparation to reduce stool passage for the first few days. A diverting ileostomy or
colostomy is recommended when the fistula has been repaired before and failed. In the worst case, the use of an interposition flap of muscle or labial fat may be required to bring new blood supply to the area. This is especially true for patients who have undergone prior radiation. General anesthesia and prone jackknife position are beneficial. A Lone Star retractor provides excellent exposure.

Although most anorectal abscesses originate in the anal crypts, other disease entities must be considered if the pathology appears atypical. Crohn’s disease should be suspected if there are numerous complex fistula tracts associated with edematous skin tags, or if there is inflammation of the rectal mucosa. Tuberculosis is now a rare cause of anal abscesses and fistulas but has recently been observed in immigrants to America.

Hidradenitis suppurativa also may mimic cryptoglandular suppurative disease. Hidradenitis may be associated with Crohn’s disease. Close examination, however, will reveal that the disease arises from the apocrine glands of the perianal skin and not the anal crypts. Wide excision of the subcutaneous apocrine glands with vacuum-assisted wound closure (VAC) is the best method of treating this problem. Intensive hygiene to reduce levels of skin flora (usually *Staphylococcus aureus*) is needed to prevent recurrence. Mixed flora sometimes cause the problem around the anus, and this will respond to daily chlorhexidine gluconate showers. Actinomycosis should be suspected if typical sulfur-like granules are seen in the abscess cavity or fistula tract.

Pilonidal disease sometimes can be confused with a posterior perianal abscess, but careful examination should reveal that there is no communication with the anus. Hair obtained from the abscess cavity when the pilonidal abscess is drained will indicate the true nature of the disease. Unroofing of the abscess, curetting the debris in the tract, and excision of the gluteal cleft hair follicle “pits” will allow delayed secondary healing. Wound VAC therapy may be useful in particularly large wounds. Shaving of the hirsute gluteal cleft and buttocks will help prevent recurrence. Obsessive hygiene is required to heal and then maintain healing of the area. More complicated cleft transposition procedures are rarely needed to treat routine cases of pilonidal disease. The wound VAC therapy has essentially supplanted the need for large surgical flap procedures in this disease.
SEXUALLY TRANSMITTED ANAL DISEASE

In recent years, there has been a profound change in the prevalence and types of sexually transmitted diseases. Genital-anal, oral-anal, and other anal-based practices among homosexual or bisexual men and among women who engage in anal receptive intercourse account for the transmission of most of these diseases.

The incidence of other venereal diseases appears to be increasing. Although a detailed discussion of these infections is beyond the scope of this textbook, the surgeon will often be consulted for evaluation of complications of these diseases.33

Human Papillomavirus

Human papillomavirus (HPV) is the etiological agent causing venereal warts. These lesions are most common in homosexual men and can have a varied appearance, including (1) discrete warts: papillary or condyloma acuminata white lesions, usually occurring singly or in clusters at or below the dentate line; (2) circumferential wart ring lesions located at the dentate line and encompassing 60% to 100% of the anal canal; and (3) flat white epithelium: pale areas of smooth opaque epithelium that often extend cephalad to the dentate line. These latter lesions may be detected more easily by using a colposcope to magnify the anal canal. A high prevalence of histologically confirmed dysplasia in these internal lesions can be detected in asymptomatic homosexual men. Dysplasia is found in 70% of HIV-seronegative men and 85% and 90% of nonimmunosuppressed and immunosuppressed HIV-seropositive men, respectively. Dysplasia cannot be predicted by the gross appearance of the warts.

The association of dysplasia with HPV is now well recognized. There are at least 60 different HPV types. Types 6 and 11 are associated with warts and low-grade dysplasia. Types 16 and 18 have been found in cervical cancer and high-grade cervical dysplasia, and type 16 has been found in high-grade anal dysplasia and invasive cancers. HPV types 31, 33, and 35 are thought to pose a lower cancer risk.

While it is clear that HPV is implicated in the pathogenesis of anal cancer in homosexual men, the rates of progression from dysplasia to cancer in the
anal canal are unknown. Anal intraepithelial neoplasia (AIN) is believed to be a precursor of anal neoplasm. Low-grade anal squamous intraepithelial lesion (LSIL) is equivalent to AIN grade I, and high-grade anal squamous intraepithelial lesion (HSIL) is equivalent to AIN grade II or III. AIN III is defined as nuclear abnormalities that have penetrated through the full thickness of the epithelium. AIN III may be found in the pathology specimen after surgery for an unrelated problem such as hemorrhoids. One can apply 4% acetic acid to the low rectal and anal canal mucosa and perianal skin to visualize the lesions under magnification. This technique of high-resolution anoscopy can be used in high-risk individuals to prevent the development of anal cancer. Depending on the size and location of the lesion around the anus, the appropriate therapy for AIN III or HSIL is ablation of the lesions, either by excision, electrocautery, or laser. Medical options include topical 5-fluorouracil (5-FU) cream or imiquimod. Wide local excision may result in morbidity including anal stenosis or incontinence. Thus, high-risk patients should be followed closely, especially those with immunocompromise.

Chlamydial Infections

Chlamydial infections are now the most common sexually transmitted disease in the United States and they account for increasing numbers of cases of proctitis in patients who practice receptive anal intercourse. There are 15 recognized immunotypes of Chlamydia trachomatis, but for practical purposes it should be recognized that there are lymphogranulomatous-causing lymphogranuloma venereum (LGV) and nonlymphogranulomatous (non-LGV) types. The non-LGV organisms are a common cause of urethritis, epididymitis, and pelvic inflammatory disease. At least half of the genital infections previously diagnosed as “nonspecific” or “nongonococcal” are caused by non-LGV Chlamydia. Chlamydial proctitis may coexist with other rectal infections, especially gonorrhea. Several serotypes are responsible for proctitis, and serotypes L1, L2, and L3 are responsible for LGV. The pathogen is introduced by either genital-anal or oral-anal intercourse. The non-LGV organisms are obligate intracellular parasites that can penetrate only columnar or transitional epithelium. The LGV organisms also can penetrate mononuclear cells, which may account for the prominent lymphadenopathy in patients with lymphogranuloma venereum.

Infection may be asymptomatic or may consist of nonspecific symptoms
such as anal pain, pruritus, purulent discharge, and bleeding. More severe forms of infection, especially severe proctitis, usually indicate the presence of one of the LGV serotypes. Perianal fistulas and rectovaginal fistulas may develop, with untreated cases progressing to severe rectal stricture. Two weeks after the initial symptoms, inguinal lymphadenopathy becomes predominant and the inguinal nodes may fuse together in a large mass.

The organism is an obligate intracellular organism, and rectal cultures are usually inconclusive. A biopsy of the rectal mucosa is probably the most commonly used method to confirm the diagnosis. The diagnosis of chlamydial infections used to be difficult because satisfactory culture techniques were not widely available. Diagnosis usually required the detection of rising antibody titers. The organism, however, now can be identified by using tissue culture techniques or DNA probes.

Chlamydial infections should be treated as soon as the diagnosis is suspected. The recommended treatment for non-LGV chlamydial infection is doxycycline or, alternatively, erythromycin for 7 to 14 days. LGV chlamydial infection should be treated with tetracycline and sulfonamides for a minimum of 21 days.

Sexual abstinence until eradication with antibiotics, education, testing, and treatment of sexual partners is recommended.

Herpes Simplex Virus

Anorectal herpes is usually caused by the type 2 herpes simplex virus (HSV-2), although the HSV-1 virus is responsible for approximately 10% of anal infections. Patients who have been previously infected have virus-specific antibodies. The first symptoms of infection are perianal pruritus or paresthesia, followed by intense anal pain. Small vesicles surrounded by red areolas may appear. These vesicles subsequently rupture, leaving small ulcers that appear on the perianal skin, in the anal canal, or even on the rectal mucosa. Fever and malaise are frequently present. The ulcerated lesions may become secondarily infected, with increased pain and discharge. The lesions usually heal in about 2 weeks. Unfortunately, a chronic relapsing course is common, although recurrent lesions are usually much less painful.

Scrapings from the base of a ruptured vesicle can be stained to show typical intranuclear inclusion bodies, but the diagnosis is most expeditiously
made by viral HSV culture.

There is no known cure for herpes. Primary or initial infections are treated with oral acyclovir, famciclovir, or valacyclovir for 7 to 10 days. Acyclovir should be taken at the onset of recurrent symptoms, which may reduce the formation of new vesicles. Chronic suppressive therapy or self-initiation of antiviral treatment with recurrent episodes may be helpful in patients with more than six recurrences per year. AIDS patients with perianal herpes resistant to acyclovir may benefit from two newer compounds, foscarinet or vidarabine.

Patients are contagious while the lesions are present and should abstain from sexual activity until all lesions are completely healed. Even after the lesions have completely healed, a condom should be used during sexual intercourse.

**Gonorrhea**

Anorectal infections caused by the bacterium *Neisseria gonorrhoeae* are common in the male homosexual population and frequently accompany other venereal diseases. Over half of homosexual men seen in screening clinics have been found to be infected, with the rectum being the only site infected in about half of cases. The majority of these infections are asymptomatic.

Symptoms vary from none to intense anorectal pain and tenesmus accompanied by a viscid, yellow anal discharge. Anoscopy may reveal anusitis or distal proctitis. Diagnosis is confirmed by obtaining cultures from the rectal discharge or mucosa, or more recently by DNA probes.

Treatment should be initiated if the disease is suspected. Untreated rectal gonorrhea can lead to septic arthritis, endocarditis, perihepatitis, and meningitis, as well as infection of sexual partners. Several drugs (penicillin, tetracycline, ampicillin, and spectinomycin) may be used for treatment, although increasing numbers of resistant strains are being recognized. Cultures should be repeated after treatment is completed, because antibiotic therapy may fail in as many as one-third of the patients. All sexual contacts also must be treated. All patients with confirmed rectal gonorrhea should have a serologic test for syphilis 3 months after treatment is completed.

**Syphilis**
The classic lesion of primary syphilis is a chancre on the genitalia, but in homosexual males the chancre usually presents in the anal canal or at the anal verge. These ulcerated lesions may mimic an anal fissure, but an aberrant location of the lesion (eg, lateral anus instead of midline) should arouse suspicion. Classic descriptions indicate that the syphilitic chancre is a painless lesion, but anal chancres may be extremely painful. The causative organism is the spirochete, *Treponema pallidum*, which may occasionally cause severe proctitis without an accompanying chancre. Inguinal adenopathy is common.

Early syphilis can be diagnosed by examining scrapings from the base of the chancre with dark-field microscopy; these lesions teem with spirochetes that can be seen as corkscrew-shaped motile fluorescent yellowish-green organisms. Serology is also very helpful in establishing the diagnosis. In untreated primary syphilis, the Venereal Disease Research Laboratory assay is reactive in about 75% of cases, in early latent syphilis about 95%, and in the secondary state it is 100% reactive. The fluorescent treponemal antibody absorption test usually becomes positive about 4 to 6 weeks after the initial infection. Rapid plasma reagin and darkfield microscopy are the appropriate tests for suspected early syphilis.

The second stage of anal syphilis appears 6 to 8 weeks after the chancre has healed in untreated patients. It may present as condyloma latum, a pale-brown or flesh-colored flat verrucous lesion, or as a mucocutaneous rash. All three serologic tests for syphilis will be positive at this stage. Skin lesions are highly contagious.

Benzathine penicillin G is the treatment of choice for syphilis. Alternative treatments include doxycycline, tetracycline, or erythromycin. Patients with syphilis must abstain from sexual contact until treatment is complete. All sexual contacts within the preceding 90 days should be prophylactically treated.

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INTRODUCTION

Constipation and fecal incontinence are 2 forms of evacuatory dysfunction that cause significant morbidity across ages and populations. Both are end symptoms of a range of etiologies that are often linked. Diagnosis and treatment depend on a detailed examination and careful workup. Some etiologies are easily treated, whereas others require extensive therapy in a multidisciplinary setting.

CONSTIPATION

Constipation is a broad term used by both patients and practitioners, with variable meaning. The Rome III definition of functional constipation requires 12 weeks of symptoms in the past 6 months, including at least 2 of the following symptoms: straining at defecation on at least 25% of defecations, lumpy or hard stools in at least 25% of defecations, sensation of incomplete evacuation for at least 25% of defecations, sensation of anorectal
obstruction/blockage for at least 25% of defecations, manual maneuvers to facilitate at least 25% of defecations (eg, digital evacuation, support of the pelvic floor), and less than 3 defecations per week (Table 53-1).¹

**TABLE 53-1: ROME III CRITERIA FOR FUNCTIONAL CONSTIPATION**²

Must include 2 or more of the following:

- a. Straining during at least 25% of defecations
- b. Lumpy or hard stools in at least 25% of defecations
- c. Sensation of incomplete evacuation for at least 25% of defecations
- d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
- e. Manual maneuvers to facilitate at least 25% of defecations (eg, digital evacuation, support of the pelvic floor)
- f. Fewer than 3 defecations per week.

Loose stools are rarely present without the use of laxatives

Insufficient criteria for irritable bowel syndrome

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² Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

**Pathophysiology and Etiology**

Multiple conditions and medications can result in functional constipation. Colonic motility, rectal sensation, distention, and propulsion aided by pelvic floor relaxation must all work in concert for stool to develop normally and pass through the colon, rectum, and anus. Constipation can be classified into 3 broad subtypes: constipation-predominant irritable bowel syndrome (IBS-C), colonic transit disorder, and obstructed defecation syndrome (ODS). Differentiating between these 3 main etiologies requires a careful history and tailored evaluation.

IBS-C is a functional gastrointestinal disorder characterized by recurring symptoms of abdominal pain, bloating, and altered bowel habits. Irritable bowel syndrome (IBS) is suspected by recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months associated with 2 or
more of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool. IBS symptoms are not treated surgically. 

Colonic transit disorder is a gastrointestinal dysmotility syndrome. Symptoms suggestive of slow transits include long intervals between bowel movements, bloating, abdominal distention, megacolon, colonic fecalization, and secondary small bowel obstruction due to constipation.

ODS is associated with a range of symptoms including incomplete and/or painful evacuation, excessive straining, sensation of incomplete evacuation, and the need to insert a finger into the vagina or anus in order to evacuate bowel contents (ie, “splinting”). ODS accounts for 50% of constipation cases and is most commonly seen in women older than age 65 years.\(^2\) It has a 60% association with both depression and anxiety.\(^3\)

**Diagnosis and Evaluation**

The above subtypes of constipation are not mutually exclusive and often coexist. In absence of alarm symptoms, such as new onset of symptoms at 50 years or older, unintentional weight loss, nocturnal diarrhea, anemia, bloody stools, family history of colon cancer, celiac disease, or inflammatory bowel disease, patients can be initiated on an empiric trial of fiber therapy, especially if their symptoms appear consistent with IBS-C.\(^4\) However, if routine medical therapy fails, further diagnostic testing should be considered to further determine the etiology of constipation.

Initially, the evaluation should always be guided by a careful history and a complete perianal and anoscopic examination. This will help rule out alternative pathology such as hemorrhoids, anal stricture, rectal stricture, or rectal prolapse. Laboratory studies for thyroid hormone and calcium levels can exclude metabolic etiologies of constipation. Endoscopy can evaluate for obstructing colonic lesions, diverticular strictures, or inflammatory bowel disease. In absence of obvious obstruction, subsequent workup of constipation should attempt to exclude functional constipation. To accomplish this, patients should undergo anorectal physiology and colonic motility testing.

**ANORECTAL PHYSIOLOGY TESTING**
Anal manometry is one of the main testing procedures performed with the goal of delineating the etiology of constipation (Fig. 53-1). The test is performed with either air- or water-charged systems. Anal resting and squeeze pressures are calculated at each centimeter starting at 6 cm from the anal verge. The high-pressure zone is identified, and mean resting, maximum resting, and maximum squeeze pressures are calculated using standardized American Society of Colon and Rectal Surgeons definitions. In addition, the test includes a quantification of rectoanal inhibitory reflex (RAIR). The RAIR describes the relaxation of the internal anal sphincter with distension of the rectum. This reflex is thought to be essential for the discrimination between gas and stool and the ability to pass them independently. Notable causes for absence of the reflex include Hirschsprung disease, circumferential myotomy, and overly aggressive lateral sphincterotomy. Other relevant findings on anorectal manometry in a patient with constipation may be the presence of elevated resting and squeeze pressures, which may suggest ODS. However, the absence of elevated sphincter pressures alone does not reliably exclude outlet obstruction, and other testing for pelvic floor dyssynergia (balloon expulsion testing and electromyography) and for intermittent anatomic outlet obstruction (defecography) is recommended when this diagnosis is high on the differential.
FIGURE 53-1 Anal manometry.

BALLOON EXPULSION TESTING

Balloon expulsion testing is an easy, inexpensive way to evaluate evacuation. A balloon is inserted in the rectum and inflated to 60 mL. Patient are asked to expel the balloon on a commode, with the expectation that a normal subject should be able to do so within 1 to 5 minutes. Patients unable to expel the balloon are suspected to have outlet obstruction, otherwise not specified. The test does not differentiate between the causes of outlet obstruction.
Electromyography (EMG) aids in the diagnosis of pelvic floor dyssynergia due to a nonrelaxing puborectalis. The test can reveal a paradoxical or nonrelaxing puborectalis muscle (Fig. 53-2). A small EMG sponge containing 2 electrodes is gently positioned into the rectum and then pulled back until the recording electrodes lodges in the anal sphincter. EMG tracings are then obtained at rest, squeeze, and push. The presence of reproducible contractions when the patient attempts to push the sponge out is defined as abnormal.
DEFECOGRAPHY

Fluoroscopic defecography allows for evaluation for intermittently occurring, obstructing pathology caused by the shifting of the pelvic organs during the act of defecation. This is a dynamic, real-time study that can reveal the presence of internal intussusception, enteroceles, sigmoidoceles, and rectoceles. It is a useful test to rule out dyssynergy that would otherwise be undiagnosed. Before examination, patients are asked to drink liquid barium or Gastrografin to opacify the small bowel. A scout abdominal radiograph is then done after 1 hour to confirm that the contrast agent has reached the right colon. The patient is then positioned in the left lateral decubitus position on the fluoroscopy table. If the patient is a woman, 10 mL of barium cream is inserted into the vagina using a catheter syringe. Then approximately 400 mL of thick paste with the consistency of stool is inserted into the rectum. In women, a barium pill is taped to the perineal body. The patient is then asked to sit down in an upright position onto a specially designed radiolucent upright commode. A single image is acquired when the patient is sitting on the commode at rest. The patient is then asked to strain but hold in the contrast material while a second image is acquired. Finally, the patient is asked to try to evacuate the rectum. Defecography images are acquired during pulsed fluoroscopy at a rate of 1 per second for 30 seconds or as needed. They can also be videotaped continuously. If contrast material remains in the rectum, the patient is asked to try again, using finger manipulation or another method to aid evacuation if that is what they normally do.

In the absence of defecography equipment, which requires fluoroscopy and a radiolucent commode, dynamic upright magnetic resonance imaging (MRI) in a sitting position can be obtained. However, upright MRI machines are expensive and scarce and have a lower signal-to-noise ratio and soft tissue resolution.

COLONIC TRANSIT TESTING

A number of options are available to assess colonic transit time. The most widely available technique involves ingestion of radiopaque markers and serial abdominal radiography refined by Metcalf et al. Patients must prepare
for the test by refraining from all enemas, laxatives, and nonessential medications 2 days before the test. Capsules containing 24 radiopaque markers are ingested. An abdominal radiograph is obtained at 5 and 7 days, and colonic transit is deemed abnormal if >30% of markers are retained (Fig. 53-3). The pattern of accumulation is also diagnostics. Left-sided or rectal accumulation suggests ODS, whereas right and transverse colon distribution suggests colonic inertia. Cowlam et al\textsuperscript{9} challenged this dogma with their study of 108 patients with functional constipation. They found no correlation between the pattern of marker distribution and any of the parameters suggesting ODS.
FIGURE 53-3  Abnormal sitz markers dispersed throughout the colon, with concentration in the rectum. Interpretation would be concurrent colonic dysmotility and obstructed defecation syndrome.

The SmartPill (SmartPill Corporation, Buffalo, NY) is a new wireless pH and pressure recording capsule that allows for assessment of regional (gastric, small bowel, and colonic) and whole gut transit time without radiation. It reveals hitherto unrecognized sex differences and upper gut dysfunction in constipation. It correlates well with radiopaque markers and offers a standardized method of discriminating normal from slow colonic transit.\textsuperscript{10} Although promising, the utility and role of gut transit assessment with a capsule remain to be seen. Utilization may also be decreased by its cost and reluctance of many insurance carriers to cover the expense given lack of proven additional benefit.

SYNTHESIZING RESULTS

After evaluations guided by history, the clinician should be able to classify the patient into 1 of the following groups. It should be noted that these groups are not mutually exclusive and overlap is common.

1. Normal transit constipation with normal colonic transit and defecation; some patients will have symptoms of IBS
2. Slow transit constipation
3. Defecatory disorder (anismus/dyssynergy/ODS)
4. Combination of 2 and 3 above; clinical observations suggest patients will have features of IBS
5. Organic constipation (mechanical obstruction or adverse drug effect)
6. Secondary constipation (metabolic disorder)\textsuperscript{4}

Accurate classification is important because it will dictate management strategy.

Management

Figure 53-4 provides an algorithm for the evaluation and treatment of constipation.
FIGURE 53-4  Algorithm for evaluation and treatment of constipation. ACE, antegrade colonic enema; IBS, irritable bowel syndrome; ODS, obstructed defecation syndrome; STARR, stapled transanal rectal resection; TSH, thyroid-stimulating hormone.

MEDICAL

The hallmark of medical management is increasing fiber in a patient’s diet. Fiber can be either soluble (eg, nuts, beans, fruit, lentils, vegetables, barley) or insoluble (eg, whole wheat, whole grain, vegetables, wheat bran). Fiber supplementation can include psyllium-based products such as Metamucil or
non–psyllium-based products such as polycarbophil (FiberCon) or dextran (Benefiber). A randomized study in 275 patients revealed superior results for psyllium (10 g twice daily), but not bran, when compared with placebo at 1 month. At 3 months, bran was better than placebo. Fiber therapy can have side effects, including gas, bloating, decreased motility, and abdominal pain. The key to introducing dietary fiber supplements is to start with a low dose and slowly increase. Patients should be counseled that improvement might not be seen for 2 to 4 weeks.

Recommendations on laxative therapy suffer from a lack of strong data. Osmotic laxatives are first-line therapy and include polyethylene glycol (PEG)-based products as well as milk of magnesia. In a controlled 6-month trial with 304 patients, successful treatment was seen in 52.0% of subjects in the PEG arm and 11% of subjects in the placebo arm. Stimulant laxatives, such as bisacodyl (Dulcolax) and senna (Senocot), should be used with caution due to concern about addiction.

More recently, intestinal secretagogues such as lubiprostone and linaclotide have shown promise in the management of constipation. Secretagogues accelerate transit and facilitate defecation by stimulating efflux of ions and water into the intestinal lumen. Lubiprostone and linaclotide have shown efficacy for both chronic constipation and women with IBS-C.

**BIOFEEDBACK FOR ODS**

For patients with ODS and/or dyssynergy, biofeedback therapy should be first-line therapy. Biofeedback teaches patients to relax the anus and puborectalis during defecation. It appears to be very effective in treating ODS, with 63% of patients with constipation having improvement after ≥ 5 training sessions, 71% of patients with pelvic floor dyssynergia having improvement lasting up to 2 years after 5 sessions, and 28% of patients with ODS and internal intussusception having at least partial improvement after 2 sessions. In a systematic review, biofeedback conferred a six fold increase in the odds of treatment success when compared to medical management alone. EMG-assisted biofeedback appears to have the best results. Shim et al described predictors of biofeedback success as harder stools, shorter duration of laxative use, higher straining rectal pressure, and
prolonged balloon expulsion.

**SURGERY**

Surgery for constipation should be considered only after medical therapy has failed and symptoms severely compromise activities of daily living. Interventions are divided into procedures for slow transit constipation and those for obstructed defecation. Some patients may need a combination of the 2 based on their individual presentation and testing results.

**Procedures for Treating Slow Transit Constipation**

**Subtotal Colectomy.** For patients with documented severe slow transit constipation without ODS, a subtotal colectomy with ileorectal anastomosis should be strongly considered. This procedure has been shown to reliably increase bowel movement frequency in patients with slow transit constipation.\(^{21}\) Although functional outcomes are generally good, patients may report persistent abdominal pain (41%-52%), postoperative incontinence (21%), diarrhea (46%), and recurrent constipation (0%-33%).\(^{22,23}\) However, most patients are satisfied with the results and state they would undergo subtotal colectomy again if given a second chance.\(^{24}\) Proper patient selection is crucial to the success of surgery.

**Sacral Nerve Stimulation.** First developed for urinary and fecal incontinence, the use of sacral nerve stimulation (SNS) to treat both slow transit and pelvic floor constipation has increased, especially in Europe. In the largest study to date, 39 (87%) of 45 patients who received SNS achieved treatment success. Colonic transit normalized in half of patients with baseline slow transit.\(^{25}\) However, in the intent-to-treat population of 48 patients, only 14 (29.2%) met the definition of a successful outcome at a median of 25 months.\(^{26}\) SNS has yet to be approved for use for constipation in the United States by the US Food and Drug Administration (FDA).

**Antegrade Colonic Enema.** Antegrade colonic enema involves creation of either an appendiceal conduit or an indwelling cecostomy catheter followed by regularly scheduled instillation of either water or PEG solution.\(^{27,28}\) This procedure is most frequently used in the pediatric population, and adult data
are limited but encouraging.\textsuperscript{29}

**Stoma.** For patients with slow transit constipation accompanied by bloating and abdominal pain, an ileostomy can be both destination therapy and a diagnostic tool to determine if symptoms are attributable to the small or large intestine. In general, in these situations, a concomitant colectomy is not recommended.

**Procedures for Treating Constipation due to Intermittent Anatomic Obstructed Defecation.** For patients with ODS, the next step is to decide who needs an operation and who will benefit from other therapy. Regardless of whether or not an anatomic cause of ODS is identified on defecography, surgical intervention is only considered in patients who failed medical management and $\geq 6$ biofeedback training sessions. This is due to the thought that anatomic ODS may be secondary to inciting dyssynergia, which needs to be treated first.\textsuperscript{30} In a prospective cross-sectional cohort study of 270 ODS patients, Hicks et al\textsuperscript{31} found that 71.1\% of patients with ODS and a coexisting rectocele responded to medical management and biofeedback alone and therefore avoided surgery.

**Botulinum Toxin Type A (Botox).** To augment biofeedback teaching and retraining, botulinum toxin type A (BTX-A; Botox) injections have been proposed as a method to induce chemical denervation of the puborectalis. Results are mixed. Ron et al\textsuperscript{32} studied 25 patients who underwent injections. Although 75\% achieved manometric relaxing, only 29.2\% had symptomatic improvement on a straining index. Faried et al\textsuperscript{33} studied 60 patients with anismus and randomized them to either biofeedback, BTX-A, or partial division of puborectalis (PDPR). The groups differed significantly regarding clinical improvement at 1 month (50\% for biofeedback, 75\% for BTX-A injection, and 95\% for PDPR), and differences persisted at 1 year (30\% for biofeedback, 35\% for BTX-A injection, and 70\% for PDPR). Constipation scores of the patients significantly improved after PDPR and BTX-A injection.\textsuperscript{33}

**Stapled Transanal Rectal Resection (STARR).** STARR was designed to treat the anatomic abnormality of internal intussusception and/or rectocele. Two circular staplers are used sequentially to perform an anterior and posterior
full-thickness rectal wall resection ultimately producing a circumferential transanal resection of the rectum. This eliminates the obstruction caused by the intussuscepting rectum and/or rectocele into the anus and the ODS attributable to these. Functional outcomes are reported as excellent in some studies, with 80% to 90% resolution of symptoms. However, subsequent studies have not been able to replicate that success and describe persistent symptoms in 35% to 44% of patients. Large rectoceles, anismus, sense of incomplete evacuation, pelvic floor descent, and digitation predict poor outcomes.

**Ventral Rectopexy.** Ventral rectopexy involves suspension of the anterior rectum to the sacral promontory with mesh. Good results have been reported in the literature. In one study, D’Hoore et al performed ventral rectopexy in 50 patients for both incontinence and ODS. In 28 of 31 patients with incontinence, there was a significant improvement in continence. Symptoms of obstructed defecation resolved in 16 of 19 patients. During follow-up, new onset of mild obstructed defecation was noted in only 2 patients. Follow-up studies have confirmed excellent outcomes. In a study of 100 patients undergoing laparoscopic ventral rectopexy for both fecal incontinence and/or constipation, constipation improved in 82 (92%) of 89 patients.

**Stoma.** For patients with isolated severe outlet obstruction, end colostomy can be considered. As stated earlier, when a slow transit component exists as well, an ileostomy is more appropriate.

**Conclusion**

Constipation is a multifactorial disorder. Differentiation between subtypes is essential for accurate diagnosis and can be achieved with careful attention to the reported symptoms and thoughtful approach to testing. Aggressive medical management is always the first, second, and third step. Many patients with ODS symptoms will also benefit from biofeedback. Surgery is an option of last resort with borderline efficacy. Patient collaboration with treatment is essential in ensuring long-lasting success.

**FECAL INCONTINENCE**
Fecal incontinence is an emotionally devastating medical disorder that can affect both men and women. Seen in up to 25% of elderly women, it is also common in those who have experienced traumatic or obstetric injury. Although not life threatening, fecal incontinence can result in a serious decrease in quality of life, resulting in depression, agoraphobia, and anxiety, and the effect on quality of life correlates with the severity of the condition. Treatment is guided by a focused workup and can result in lasting improvement. Even incremental improvements in severity are meaningful given the gradient in the impact on the quality of life.

**Etiology and Pathophysiology**

Normal continence has several components. Rectal capacitance and compliance are essential for normal defecation. The rectum normally holds between 200 and 250 mL. It has limited muscular activity intrinsically and distends readily with filling. The internal anal sphincter provides 80% of the resting anal sphincter pressure that provides the resistance to gas and mucus at the anal canal. The sampling reflex is a function of rectal distension causing internal anal sphincter relaxation via an intermural reflex to the internal sphincter. The contents of the rectum can then be sensed in the sensory nerve–rich transitional zone and anoderm to discriminate the true nature of rectal contents. This sampling reflex occurs throughout the day to provide continence and also serves to initiate the defecation process. The voluntary external sphincter muscle contraction in response to this sampling reflex provides the final active component of fecal continence. The subconscious, voluntary contraction of the external sphincter, puborectalis, and pelvic floor muscles provides complete control of rectal contents. The pelvic floor muscles maintain continuous activity, even during sleep, to provide fecal continence.

Fecal incontinence is defined as the inability to control the passage of gas, liquid, or stool until a socially acceptable time and place for evacuation. The frequency of the incontinence may vary, and the loss of control may involve gas, liquid stool, or solid stool. Frequent episodes of incontinence of gas alone can be just as debilitating as passage of stool. Evaluation of incontinence must include assessment of both severity of disease and impact on quality of life. A number of well-validated, easy-to-use surveys are available for both clinical and research use.\(^ {41,42} \)
The etiology of fecal incontinence is often multifactorial and requires thoughtful evaluation. A review of the 2005–2006 National Health and Nutrition Survey found progressive incidence of fecal incontinence with increasing age from 2.9% in women 20 to 39 years old to 21.6% in women > 80 years old. Anal weakness can be the end result of a multitude of etiologies (Table 53-2). Mechanical disruption due to trauma results in division or damage to the external sphincter muscle. Neurogenic incontinence results from stretching of the pudendal nerves from prolonged labor, descent of the perineum and nerve stretch during straining during defecation, or rectal prolapse. Idiopathic incontinence is seen in patients with medical diseases such as diarrhea or inflammatory bowel disease or patients who use sedatives that cause poor sensation in the anal canal.

### TABLE 53-2: ETIOLOGY OF FECAL INCONTINENCE

<table>
<thead>
<tr>
<th>Trauma</th>
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<tbody>
<tr>
<td>Obstetric trauma</td>
</tr>
<tr>
<td>Anorectal surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomic disturbances of pelvic floor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectocele</td>
</tr>
<tr>
<td>Rectal prolapse</td>
</tr>
<tr>
<td>Internal intussusception</td>
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</tbody>
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<thead>
<tr>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Inflammatory conditions/diarrhea</td>
</tr>
<tr>
<td>Central nervous system disease/neuropathy</td>
</tr>
</tbody>
</table>

| Internal sphincter thinning of unknown etiology |

### Diagnosis and Evaluation

Evaluation begins with a thorough history, including frequency and duration of incontinence. History of anal trauma, including surgical and obstetric, should be obtained. Patients should also be queried for a history of scleroderma, inflammatory bowel disease, and neurologic disease. After a careful physical exam including a rectal exam and anoscopy, patients may
benefit from manometry, pudendal nerve terminal motor latency, anorectal ultrasound, and potentially defecography.

Keating et al\textsuperscript{44} demonstrated the limitations of mere history and physical exam in the diagnosis of fecal incontinence. In his study, 50 patients with fecal incontinence were seen by 2 physicians who diagnosed etiology and suggested treatment based on traditional evaluation alone. Patients then underwent anorectal physiology testing and ultrasound. The plan had to be changed in 20% of patients.\textsuperscript{44}

**MANOMETRY**

Anorectal manometry provides essential functional information about the anal sphincters. Details about manometric evaluation have been discussed earlier in this chapter. In the evaluation of fecal incontinence, a number of different patterns can be recognized in manometric pressures. Normal mean resting pressure in an adult ranges from 40 to 70 mm, and a large percentage of this comes from the internal anal sphincter. Patients with fecal incontinence often have low resting pressure. Mean squeeze pressure is normally 2 to 3 times the resting value and is mostly provided by the external sphincter. As such, damage to the external sphincter from childbirth or surgery can cause decreased squeeze pressure. Rectal sensation is measured by slowly inflating a balloon in the rectum. Normal volunteers normally encounter sensation at 40 mL of air. Patients with overflow incontinence often require higher volumes to generate sensation. Finally, rectal compliance is the measured change in pressure in response to change in volume within a water-filled or air-filled balloon within the rectum. Patients with a noncompliant rectum can develop fecal incontinence because their rectum is unable to accommodate the stool bolus.

**PUDENDAL NERVE TERMINAL MOTOR LATENCY**

Neuropathy of the pudendal nerve is a known etiology of fecal incontinence. Testing of the pudendal nerve terminal motor latency (PNTML) is a necessary component of the evaluation of fecal incontinence. A disposable electrode is attached to the practitioner’s finger, inserted into the anus, and directed toward the ischial spines bilaterally. Electrical impulses are then delivered to the pudendal nerve, and the time for response at the external
sphincter is measured. Normal response is within 2.0 ± 0.2 milliseconds. Ricciardi et al. showed that the majority of incontinent patients with intact sphincters have abnormal PNTML. Bilateral, but not unilateral, prolonged PNTML is associated with poorer function and physiology in the incontinent patient with an intact sphincter. Loganathan et al. related PNTML to manometry and showed that in patients with an intact anal sphincter, either unilateral or bilateral prolonged PNTMLs are associated with significantly decreased resting and squeeze pressures. This suggests that both internal and external sphincter function is impaired with pudendal nerve injury and that the inhibition of internal sphincter function may be due to damage of autonomic, principally sympathetic fibers carried in the pudendal nerve.

**ANAL ULTRASOUND**

Anal ultrasound is a technique to image the internal and external anal sphincter muscles as well as the puborectalis muscle. After an enema and a digital rectal exam, a rigid rotating probe with a 360-degree radius and an ultrasound frequency of between 5 and 16 MHz is introduced into the rectum. The probe is then slowly withdrawn so that the pelvic floor and sphincter complex are completely visualized. Recent software allows for 3-dimensional reconstruction of the images.

Anal ultrasound assesses muscle thickness and integrity. Scarring, loss of muscle tissue, or other local pathology can all be identified (Fig. 53-5). Internal sphincter defects tend to be identified more reliably than external defects. Like other varieties of ultrasound, the quality of the examination is markedly operator dependent. When relating ultrasound findings to manometry, defects in the internal sphincter are accompanied by lower resting pressures, while defects in the external sphincter are associated with lower maximum anal squeeze pressures. In addition, the size of the external anal sphincter defect inversely correlates with the maximum squeeze pressure.
FIGURE 53-5  External sphincter defect. Note associated internal sphincter tear and retraction.

DEFECOGRAPHY

With normal results in the above testing, fluoroscopic defecography can be helpful in identifying cryptic causes of fecal incontinence. Internal intussusception or intermittent rectal prolapse may weaken the anal sphincters and result in incontinence. Defecography can also identify incomplete evacuation, which might suggest overflow incontinence as a cause of symptoms. The technique is described above.

Management

Figure 53-6 provides an algorithm for the evaluation and treatment of fecal incontinence.
FIGURE 53-6 Algorithm for evaluation and treatment of fecal incontinence. FIQoL, Fecal Incontinence Quality of Life Scale; FISI, Fecal Incontinence Severity Index; MRI, magnetic resonance imaging; PNTML, pudendal nerve
terminal motor latency; SNS, sacral nerve stimulation.

**MEDICAL**

Before consideration of surgical treatment, management of fecal incontinence should first begin with fiber supplementation to increase stool consistency, loperamide to decrease stool frequency, and amitriptyline to increase rectal sensory thresholds to fecal stimulation. Patients should also be instructed in bowel evacuation protocols using daily evacuation with glycerin suppositories. All patients with diarrhea should have a thorough workup and treatment of diarrhea, with treatment tailored to its etiology.

**BIOFEEDBACK**

Biofeedback uses visual, auditory, and sensory information to improve a patient’s ability to sense rectal fullness and retrain appropriate sphincter contraction. Engel et al\textsuperscript{51} published the first report of the technique in 1974, using a Miller-Abbott balloon as a sensor attached to a polygraph to improve the quality of Kegel exercises. Heymen et al\textsuperscript{52} assigned 108 patients to either biofeedback or pelvic floor exercises. Biofeedback training increased anal canal squeeze pressure more than pelvic floor exercises. Three months after training, 76\% of patients treated with biofeedback versus 41\% of patients treated with pelvic floor exercises reported adequate relief.\textsuperscript{52} Current treatment is variable and can include weekly or biweekly sessions of 30 to 60 minutes each on a number of different machines. Jodorkovsky et al\textsuperscript{53} highlighted the difficulty in biofeedback, with less than half of patients recommended for biofeedback ultimately undergoing therapy. Byrne et al\textsuperscript{54} studied 513 patients and found a 70\% improvement rate in the short term. Treatment success was more likely in patients who completed 6 training sessions, were female, were older, or had more severe incontinence. Patients were less likely to complete treatment if they were male, were younger, or had milder incontinence.\textsuperscript{54} Biofeedback should be considered a first-line option for most patients with fecal incontinence who have not responded to simple dietary modification or medication.\textsuperscript{55}

**SURGERY**
In determining the correct procedure for patients with fecal incontinence, the lack of high-quality data on the surgical treatment for fecal incontinence in adults is striking. In many situations, treatments are offered in a sequence from simple to complex with the goal of minimizing complications while aiming to achieve an improvement in symptoms. Treatments are classified based on 1 of 3 goals: bulking the sphincter complex; reconstruction of the sphincter complex; or rewiring the defecatory neuromuscular pathway. Finally, some patients with fecal incontinence have internal or external rectal prolapse, which needs further evaluation and treatment. Finally, when all else fails, stoma and stoma alternatives can be considered.

**Bulking or Remodeling the Sphincter Complex**

**Secca.** In patients with mild to moderate fecal incontinence who have failed fiber and biofeedback and do not have an identifiable sphincter defect, the Secca procedure is a therapeutic option. The Secca procedure involves the administration of radiofrequency to the anal canal in an attempt to cause thermal injury to the sphincters. In theory, radiofrequency-induced injury to the internal anal sphincter causes collagen deposition and fibrosis with the potential for tightening of the affected area. It can be performed in the outpatient setting with minimal morbidity. Patients are placed in the jackknife prone position, and the probe is placed in the anal canal so that the electrodes are at the level of the dentate line. Radiofrequency is then delivered to approximately 16 to 20 sites throughout the anal canal. Ruiz et al studied 24 patients and collected 12-month follow-up data on 16 patients. A Fecal Incontinence Score improved from a mean of 15.6 (± 3.2) at baseline to 12.9 (± 4.6) at 12 months. Takahashi et al provided even longer follow-up when they studied 19 patients for 5 years. At the 5-year follow-up, the mean fecal incontinence score had improved from 14.37 to 8.26, with 16 patients (84.2%) demonstrating >50% improvement. All fecal incontinence–related quality of life scores improved.

**Injectable Bulking Agents.** For patients with minor fecal incontinence due to internal anal dysfunction, injection of various biocompatible bulking agents has been shown to be modestly effective, although so far, only NASHA Dx (non–animal-stabilized hyaluronic acid/dextranomer) is FDA approved for use in the United States. Injection of NASHA Dx is a simple, noninvasive
procedure that can be performed in an outpatient setting. The bulking gel is injected into the anal submucosa, above the dentate line. It is thought that the injection increases the resting anal sphincter pressures by mass effect, as well as by restoring anal symmetry. FDA approval of the agent was granted after Graf et al randomized 206 patients to either NASHA Dx or sham injection. Seventy-one patients who received NASHA Dx (52%) had a 50% or more reduction in the number of incontinence episode, compared with 22 patients who received sham treatment (31%). They recorded 128 treatment-related adverse events, of which 2 were serious (1 rectal abscess and 1 prostate abscess).

In general, patients considered for both Secca and NASHA Dx injections should first undergo Secca. The goal is to avoid subsequent superinfection of NASHA Dx if the Secca radiofrequency needles are deployed through the implant. Though there have been no reports of adverse events with Secca following NASHA Dx injection, this remains a preferred sequence of interventions.

**Reconstruction of the Sphincter Complex**

*Sphincteroplasty*. In the appropriately selected patient, sphincter repair can reduce and even cure fecal incontinence (Fig. 53-7). The overall success rate is around 60%, and patients should be selected based on normal PNTMLs, reduced anal sphincter pressure on manometry, and a sphincter defect on ultrasound. The operation is best performed in the jackknife prone position. An elliptic incision on the perineal body is made, and the rectum is separated from the vagina all the way to the levators. The external anal sphincter is identified and freed to allow for overlap of the edges (Fig. 53-8). Slowly absorbable sutures are then used to approximate the scar and muscles in the overlapped position. The repair is covered with interrupted sutures, and the skin is closed loosely. Barisic et al examined 65 patients undergoing overlapping anal sphincter repair; 72.3% were a result of obstetric trauma. At a mean follow-up of 80 months, 55.5% of patients reported excellent results. Bravo et al followed 191 patients for 10 years and noted that results worsened significantly between the assessments at 3 and 10 years, with only 6% of patients reporting no incontinence at 10 years. Gearhart et al studied 20 women with large sphincter defects (>50%) and noted that overlapping anal sphincter repair improved absolute resting and squeeze pressures and
Fecal Incontinence Severity Index scores. In addition, patients with lower scores had higher increases in their pressures postoperatively.\(^{64}\)

**FIGURE 53-7** Anal sphincter overlapping muscle repair. **A.** Anterior incision and perineal view of muscles. **B.** Rectal flap is created, and sphincter muscles are isolated. **C.** Muscle flaps are fully mobilized. **D.** Muscle flaps are overlapped around a 15-mm rubber dilator or fingertip. **E.** Muscle flaps are sutured in place, and the perineal body is repaired. **F.** A drain is placed behind the vaginal wall and the wall closed. (Reproduced with permission from Zuidema GD: Shackleford’s Surgery of the Alimentary Tract, 4th ed. Philadelphia, PA: WB Saunders; 1996.)
Artificial Bowel Sphincter. For patients who fail all other treatments, an artificial sphincter of silicone with a water-filled circumanal cuff may be implanted. The fluid is shifted from the sphincter-encircling cuff to a balloon implanted in the space of Retzius. The 2 reservoirs are connected via silicone tubing. The artificial bowel sphincter (ABS) has produced good results and has been FDA approved for nearly 2 decades. In patients who can tolerate device implantation without complications, overall results of ABS are excellent, with 85% of patients reporting complete or near-complete continence to solid stool. However, if results are measured on an intent-to-treat basis, the success rate was 53%, mostly due to the need to explant devices that become infected or break.⁶⁵ Even with improved experience, the incidence of surgical revision and explantation remains high, highlighting the importance of careful patient selection (Figs. 53-9 and 53-10).⁶⁶
FIGURE 53-9  Patient needs artificial bowel sphincter revision because anal cuff snapped open and it is not encircling the anus circumferentially.
Magnetic sphincter augmentation, which is currently not FDA approved, may ameliorate some of the concerns regarding the frequent need for device explanation seen with traditional ABS breakage while providing equivalent benefits (Fig. 53-11). In the largest study to date, 18 patients were implanted with the magnetic sphincter augmentation device. Bowel diary results showed that 76% of the patients with implants experienced a ≥50% reduction in the number of fecal incontinence episodes per week. Further study on this device is required.
Rewiring the Defecatory Neuromuscular Pathway

**Sacral Nerve Stimulation (SNS).** SNS was initially developed for urinary incontinence before Matzel et al.\(^6^9\) described its use for fecal incontinence. The goal is stimulation of the sacral nerves to recruit additional inactive motor units to improve muscle strength, resulting in an increase in resting anal pressure.\(^7^0\) SNS is offered to all patients who do not have a large sphincter injury that may be amenable to a simpler sphincter repair and who report loss of a full bowel movement more than twice a week. It is a 2-stage procedure, with the first stage involving percutaneous nerve evaluation, which typically lasts 2 weeks. Patients who experience a 50% or greater decrease in the number of incontinence episodes are then offered placement of a permanent stimulator. The procedure is performed using fluoroscopy.
under sterile conditions. (Fig. 53-12). Stimulation of the S4 nerve roots via the sacral foramina is tested, and a permanent stimulator is placed. Results reported in the literature are encouraging. Wexner et al\textsuperscript{71} studied 129 patients who underwent a 2-week trial of subchronic test stimulation. One hundred and twenty patients qualified for permanent implant, and 112 patients were implanted. The mean follow-up time was 28 months, and more than 75\% of patients noted persistent benefits including a 50\% decrease in weekly incontinence episodes, incontinent days, and urgent incontinent episodes.\textsuperscript{71} Altomare et al\textsuperscript{72} reported even more robust follow-up of 272 patients who underwent SNS placement with a long-term follow-up at a median of 84 months. Significant reductions in the number of fecal incontinence episodes per week and summative symptom scores were recorded after implantation and maintained in long-term follow-up. Risk of long-term failure correlated with minor symptom score improvement during the temporary test phase.\textsuperscript{72}
FIGURE 53-12 A and B. Sacral nerve stimulation implantation can be performed under local anesthesia.

**Posterior Tibial Nerve Stimulation.** Posterior tibial nerve stimulation (PTNS) is believed to work by stimulation of the ascending afferent spinal pathways. The tibial nerve contains afferent and efferent fibers originating from the fourth and fifth lumbar nerves and the first, second, and third sacral nerves. Stimulation of the tibial nerve may lead to changes in anorectal neuromuscular function similar to those observed with SNS, but without the need for a surgically implanted device. A recent systematic review found the success rate of PTNS, based on the proportion of patients who achieved a reduction in weekly fecal incontinence episodes of at least 50%, to be 63% to 82%. However, a recent randomized controlled trial of 227 patients assigned to PTNS or placebo questioned these data by showing no statistical significance when accounting for a placebo effect, which was as high as 31%.

**Stoma and Stoma Alternatives.** For patients who fail both medical and surgical therapy, a permanent end colostomy may be appropriate. Assessment of postoperative quality of life shows that patients are generally satisfied. In a series of 69 patients who underwent colostomy for fecal incontinence, 84% indicated they would “probably” or “definitely” choose to have the stoma again.

**CONCLUSION**

Fecal incontinence is a common problem and can occur in both men and women. Many forms are treatable surgically. Surgical treatment is ultimately determined by etiology. A careful, tailored workup is essential to providing the best treatment. This field is a dynamic one, and research continues on innovative techniques.

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CANCER OF THE RECTUM

Joel Goldberg • Ronald Bleday

INCIDENCE AND EPIDEMIOLOGY

At the beginning of the 21st century, rectal cancer continues to be a significant medical and social problem. Currently, there are approximately 135,000 cases of colorectal cancer diagnosed in the United States each year and 50,000 deaths. Approximately 60% of all cases occur in patients older than 65 years of age. Cases that occur prior to age 65 this include 45% of men and 39% of all women diagnosed with colorectal cancer. Significant racial disparities also exist in the incidence and mortality for colorectal cancer, with non-Hispanic blacks (NHB) having the highest incidence and mortality. When compared to non-Hispanic whites (NHW), the NHB population has a 20% higher incidence of colorectal cancer and a 40% higher mortality rate. Overall survival is higher for patients with rectal cancer (67%) than colon cancer (64%), with the most likely explanation being that rectal cancer is more often diagnosed at an earlier localized stage.

Overall, 40% of colorectal tumors are in the proximal colon and 60% are in the distal colon and rectum. However, women are more likely to have proximal lesions (46%) when compared to men (37%), and this disparity increases with advancing age. At younger ages (less than 50), both men
(41%) and women (36%) are more likely to be diagnosed with rectal than colon cancer. In fact, there has been a substantial absolute increase in the risk of rectal cancer in patients born after 1970. The reason for the increased risk for rectal cancer in this young population has not been identified but is most likely related to a change in environment, either an exogenous exposure or ingested material in foods such as pesticides or food additives. Increases in the sedentary lifestyle, high-fat diet, and obesity have been suggested etiologic factors as well. As pointed out above, adenocarcinoma of the rectum accounts for nearly 30% of all colorectal cancers. This translates into about 41,000 new diagnoses of rectal cancer each year and greater than 10,000 deaths attributable to this disease within the same time.\textsuperscript{1,2}

**HISTORY**

The history of modern rectal cancer resection dates to 1884, when Czérny described the first abdominoperineal resection (APR). In 1885, Kraske pioneered the transsacral approach of rectal resection and anastomosis. In 1908, Miles improved on the APR by understanding that there was a “zone of upward spread.”\textsuperscript{3} He emphasized the importance of performing a wide perineal excision. Consistent with this, current surgical technique includes a cylindrical resection at the level of the levators to include the entire anal canal such that there is not a “coning in” or “waist” on the specimen at the distalmost aspect of the specimen. Furthermore, Miles advocated removal of the rectum with a high ligation of the superior hemorrhoidal artery as well as excision of the abdominal attachments of the rectum and the iliac lymph nodes. Despite the improvements in oncologic resection, operative mortality in Miles’ first series exceeded 42%. Over the next 80 years through the late 1980s, mortality and morbidity for rectal cancer surgery improved markedly in pace with improvements in intra-, peri-, and postoperative care. Unfortunately, there were few, if any, advancements in oncologic techniques during this period. Then, in the late 1980s, William Heald described and began popularizing total mesorectal excision (TME) for carcinoma of the rectum.\textsuperscript{4} In this technique, he advocates using sharp dissection to perform the complete excision of the mesorectum and its associated lymphatics along the subtle fascial planes that encompass the rectum. Moreover, Heald described a “zone of downward spread” within the mesorectum that requires complete
excision to reduce local recurrence. Finally, local excision of small rectal cancers has been used for over 100 years in selected patients. More recently, local excision is being combined with neoadjuvant and adjuvant chemoradiotherapy to maximize local control with a minimally invasive approach.

**ETIOLOGY AND RISK FACTORS**

In Western industrialized nations, the average lifetime risk for an individual to develop colorectal cancer is approximately 6%. This risk increases two- to fourfold if the patient has a personal history of a first-degree relative with colorectal cancer. Inflammatory bowel disease (IBD) is another risk factor. In the first 10 years after the initial diagnosis of ulcerative colitis (UC), the incidence of colorectal cancer increases, and in the past was suggested to be as high as 1% per each year of disease. Recent studies, however, have demonstrated that the cumulative risk is about 2% to 7.5% at 25 to 30 years of disease duration and as high as 13.5% at 45 years of disease. Pancolitis is associated with both an earlier and an increased risk for colorectal cancer when compared to left-sided colitis alone. Screening the colon yearly starting at 10 years after the diagnosis with colonoscopy and multiple biopsies in four quadrants every 10 cm from the cecum to the distal rectum is used to predict when a patient is at risk for developing colorectal cancer. If high-grade dysplasia is detected in any of the biopsies, the patient should be advised to have a total proctocolectomy. Some practitioners advocate a surgical resection for low-grade dysplasia as well, whereas some are willing to repeat a colonoscopy with multiple biopsies. If low-grade dysplasia is found on subsequent short-interval colonoscopy, then total proctocolectomy is advised. Ultimately, the most effective method for preventing colon cancer in patients with UC is to remove the colon once any type of dysplasia has been identified. Crohn’s colitis is also associated with an increased risk for colorectal cancer. This is often not appreciated by clinicians because patients with severe Crohn’s colitis often undergo proctocolectomy before their long-term risk becomes an issue. The cumulative risk for colon and rectal cancer in patients with Crohn’s colitis is 2.9% at 10 years, 5.6% at 20 years, and 8.3% at 30 years. Genetic risk factors also have been implicated in the development of
colorectal cancer. One is familial adenomatous polyposis (FAP), an autosomal dominant syndrome with 100% lifetime risk of developing colorectal cancer. The abnormality is caused by a defect in the $APC$ gene located on chromosome 5q21. Patients with FAP develop hundreds or thousands of adenomas by their twenties, and colorectal cancer develops in all patients by age 50 years if untreated. Extraintestinal manifestations of this genetic defect include desmoid tumors, periampullary masses, osteomas, and medulloblastomas. A second genetic abnormality associated with the development of colorectal cancer is related to defects in the mismatch repair genes $MLH1$, $MSH2$, $MSH6$, and $PMS2$. Genetic defects in these mismatch repair genes affect the repair of DNA replication errors and spontaneous base repair loss and contribute to hereditary nonpolyposis colorectal cancer (HNPCC) that is also known as Lynch syndrome. Despite the name, these cancers arise from adenomas and may account for 5% of all colorectal malignancies. In this autosomal dominant syndrome, cancers occur more often on the right side of the colon. Despite developing at a younger age, there is a better prognosis with these cancers when compared with age-matched controls with a non-HNPCC colorectal cancer. In theory, a patient with HNPCC living to age 80 years would have an 80% risk for developing colorectal cancer; additionally, there is a substantial risk of endometrial cancer (50%), ovarian cancer (15%), urinary tract cancer (10%), and gastric cancer (5%). There is a smaller but substantial risk of small intestinal (1%) and hepatopancreaticobiliary (1%) tumors as well. Family members should be screened initially at age 25 years or 10 years prior to the age at which the first family member was diagnosed with a neoplasm. Screening should include yearly colonoscopy and esophagogastrroduodenoscopy (EGD) every 3 years (unless there is a family history of gastric cancer when yearly EGD is advised). If an endoscopically unresectable polyp or cancer is detected, a total abdominal colectomy with an ileorectal anastomosis is recommended. Urine cytology to rule out dysplastic cells in the genitourinary tract (which is at risk for transitional cell carcinoma) is recommended. Women who desire to retain fertility should get at least once-yearly transvaginal pelvic ultrasounds and CA-125 levels. Any affected woman who has finished childbearing should consider having a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). Any affected woman who requires a colectomy should be advised to undergo simultaneous prophylactic TAH-BSO. Finally, there is MUTYH polyposis, which is an autosomal recessive genetic defect.
that predisposes to colon and rectal cancer as well. This is often referred to as the autosomal recessive FAP, as this disease has very similar features to FAP. Patients who are carriers of MYH genetic defects are also at increased risk of colorectal cancer even though they do not carry genetic defects in both alleles. These patients should have colonoscopy every 5 years.

Dietary fats, especially red-meat fats, have been implicated as a risk factor for colon and rectal cancer. People who consume less than 15% of their diet as fat have a lower incidence of colorectal cancer, whereas those who take in 20% of their diet as fat, either as unsaturated animal fat or as highly saturated vegetable oils, have an increased risk of colorectal malignancy.

In the past few decades, several studies have linked alcohol consumption and tobacco use with an increased risk of colorectal neoplasia. Moreover, there appears to be a synergistic effect with an even greater increased risk of adenomatous polyps in people who are both smokers and drinkers.

**POLYPS**

The concept that colorectal cancers develop from polyps, or the “adenoma-to-carcinoma sequence,” was first described by Dukes in 1926. Most patients with rectal cancer have no inherited component; instead, there is an initiating genetic mutation, such as of an oncogene like \( K_{ras} \), that leads to abnormal cell growth. Subsequently, mutations resulting in inactivation of tumor suppressor genes, such as \( p53 \), loss of heterozygosity (LOH) on the long arm of chromosome 18 and the APC gene (even in non-FAP patients), allows for progression to cancer. In fact, in sporadic cancers, mutations in the APC gene are the most common initial genetic alteration.

The time course for polyp development and transformation to cancer is thought to be 5 to 10 years. Most adenomas remain benign; however, histologic type, polyp size, and evidence of dysplasia are associated with transformation. Data from the National Polyp Study and St. Mark’s Hospital in London show that approximately 75% to 85% of adenomas are tubular, 8% to 15% are tubulovillous, and 5% to 10% are villous. Tubular adenomas usually form a stalk, whereas villous adenomas have a broad base (Fig. 54-1). Villous histology is associated with an increased risk of cancer development. Only 1% of polyps less than 1 cm in diameter show evidence of malignant transformation, whereas 50% of polyps greater than 2 cm in diameter harbor
areas of carcinoma.

**FIGURE 54-1** Haggitt classification of a pedunculated and sessile polyp, each of which contains an invasive cancer.

Clinically, it is important to diagnose the type, size, and number of polyps to risk-stratify patients for treatment and future surveillance. Endoscopic treatment likely reduces or eliminates the risk of colorectal cancer in patients. Rigid sigmoidoscopy and flexible sigmoidoscopy are all that are necessary to screen the rectum. Sigmoidoscopic screening should be followed by a complete colonoscopy if biopsy of a small rectal or sigmoid polyp shows adenomatous changes. Colonoscopy screening as the first study is indicated in high-risk populations such as those with a family history of colorectal cancer, a personal history of IBD, or a known familial genetic mutation (FAP/HNPCC/MUTYH). Autopsy studies have reported that adenomas are present in 20% to 60% of patients with a colorectal cancer, and synchronous cancers are found in 3% to 9% of patients. In patients who cannot undergo a preoperative colonoscopy, either a virtual colonoscopy or barium enema should be performed. If both procedures are contraindicated in these patients, colonoscopy evaluation should be performed 3 months after resection.
Treatment of the malignant rectal polyp is becoming more common with the increase in colonoscopy screening and the early diagnosis of small distal rectal cancers. Surgical treatment in part depends on the morphology of the polyp and the histologic evaluation of the resected lesion. Pedunculated malignant polyps are classified by Haggitt per the depth of invasion of the cancer within the head of the polyp and stalk⁹ (see Fig. 54-1). Malignant polyps completely resected with greater than 2-mm margins and without stalk invasion are considered adequately treated with colonoscopic removal, provided there are no poor prognostic histologic features such as lymphovascular invasion or poor differentiation (high grade). Tumors with poor differentiation and/or lymphatic/venous invasion are associated with an increased incidence of involved lymph nodes.¹⁰

ANATOMY

Anatomic Landmarks

The type of therapy offered to a patient with rectal cancer depends not only on the stage of the tumor but also on its location within the pelvis and its relation to the anal sphincters. Compared with colon cancer, knowledge and appreciation of anatomic landmarks are critical in determining resectability and sphincter preservation.

The rectum, usually 15 to 20 cm in length, extends from the rectosigmoid junction, marked by fusion of the taenia coli into a completely circumferential muscular layer, to the anal canal. In males, the rectum tends to be longer (18 cm) when compared to females (15 cm). The rectum transitions from being intraperitoneal to being completely extraperitoneal 10 to 12 cm from the anus and the root of the sigmoid mesentery is approximately 19 cm from the anal verge on rigid sigmoidoscopy.¹¹ The rectum is “fixed” posteriorly and laterally by Waldeyer’s fascia and the lateral stalks, respectively. In the male patient, the anterior rectum is fixed to Denonvilliers’ fascia, a fold of two layers of peritoneum that separates the rectum from the posterior prostate and seminal vesicles. In the female patient, the peritoneal cavity descends to the pouch of Douglas, with its most dependent point being adjacent to the cervix anteriorly and mid-rectum posteriorly.¹² When seen endoscopically, the rectum has three valves of
Houston, the middle of which corresponds to the anterior peritoneal reflection (Fig. 54-2A).
While many surgical descriptions for rectal cancer refer to the distance of the lesion from the anal verge or the dentate line, a more accurate description for distal (palpable lesions) is the distance above the anorectal ring as palpated by the examining surgeon. For nonpalpable lesions, we use a rigid sigmoidoscope to localize the lesion and then ascertain the distance from the anal verge to the mass. At the muscular level, the anal canal starts at the top of the “high-pressure zone” that is at the proximal aspect of the anorectal ring, a muscular structure consisting of the internal sphincter, external sphincter, and puborectalis (Figs 54-2A and B). The high-pressure zone descends beyond the dentate line to the junction of the anal mucosa and the perianal skin; this junction is often referred to as the anal verge. To achieve an adequate distal margin (≥1 cm) with sphincter preservation, the lower border of a tumor must be located high enough above the top of the anorectal ring. The closer the tumor is to the anorectal ring the less likely the surgeon will be able to get extra length with rectal mobilization. This will often make sphincter preservation more difficult. This caveat even holds true with neoadjuvant chemoradiation, as scarring in the distal rectum after radiation and a lack of mesorectum fixes the tissues posteriorly, making it technically more difficult for the surgeon to gain extra length even with mobilization down to the levator ani complex. Hence, some tumors that are 1 to 2 cm above the anorectal ring and seem at initial exam to be amenable to sphincter preservation are not. Once in the operating room, the surgeon is not able to gain distal mobilization and an adequate margin is difficult to achieve and thereby sphincter preservation can prove challenging or not possible. If curative resection compromises perfect function of the sphincter apparatus, or if an adequate distal margin cannot be obtained while preserving the anorectal ring, an APR with a permanent colostomy should be constructed. Although a patient may assume that a colostomy indicates a hopelessly incurable cancer, we must emphasize that the colostomy is necessary because of the anatomic location, not necessarily the severity of the rectal cancer.

**Vascular Supply**

Arteriography demonstrates extensive intramural anastomoses between the superior, middle, and inferior rectal arteries. The superior rectal artery
originates from the inferior mesenteric artery and descends in the mesorectum to supply the upper and middle rectum (Fig. 54-3). The inferior rectal arteries, branches of the internal pudendal arteries, enter posterolateral and provide blood supply to the anal sphincters and epithelium. The middle rectal artery, often depicted in anatomic drawings as a large and significant artery branching off the internal iliac artery on each side, is seldom greater than 1 mm in diameter. In one study, the middle rectal artery was observed in only 22% of cadaver specimens. When present, the middle rectal artery is located near the lateral rectal stalks. These stalks are primarily nerves but have been confused previously with arterial supply.

FIGURE 54-3 Vasculature of the rectum and anus. A. Arterial supply. B. Venous drainage.

The superior rectal vein drains the upper and middle thirds of the rectum and empties into the portal system via the inferior mesenteric vein. The middle rectal veins drain the lower rectum and upper anal canal into the internal iliac veins. The inferior rectal veins drain the lower anal canal, emptying into the internal iliac veins via the pudendal veins. Because the
venous systems communicate, low rectal cancers may spread via the portal and systemic circulations.

**Lymphatic Drainage**

Local recurrence after resection is common and can occur with and without distant metastatic disease. Rectal cancer can spread locally via lymphatics that follow cranially along the superior hemorrhoidal vessels. This “zone of upward spread” was described initially by Miles in his landmark paper describing the APR. Heald has described a “zone of downward spread” within the mesorectum⁴; this zone can encompass as much as 4 cm beyond the distal mucosal edge of the tumor.¹⁴,¹⁵ Although some surgeons and pathologists describe tumor within this zone of downward spread as tumor implants, others believe that these implants are replaced nodes. Appreciation of the zones of upward and downward spread has influenced the extent of dissection surgeons now perform for curative resection of rectal cancers.

Lymph from the upper and middle rectum drains into the inferior mesenteric nodes (Fig. 54-4). Lymph from the lower rectum may drain into the inferior mesenteric system or into the network along the middle and inferior rectal arteries, posteriorly along the middle sacral artery, and anteriorly through the channels to the retrovesical or rectovaginal septum, to the iliac nodes, and ultimately, to the periaortic nodes. In a Japanese study, the obturator nodes, external to the hypogastric nerve plexus, were found to be involved with cancer in 8% of tumors located in the distal rectum, whereas these nodes were rarely, if ever, involved with proximal tumors.¹⁶ Lymphatics from the anal canal above the dentate line usually drain via the superior rectal lymphatics to the inferior mesenteric lymph nodes and laterally to the obturator and internal iliac nodes. Below the dentate line, lymph drains primarily to the inguinal nodes but may empty into the inferior or superior rectal lymph nodes. In most cases of rectal cancer, spread to the inguinal lymph nodes should be considered stage IV disease. In our experience, however, some patients whose distal rectal adenocarcinoma invades the anal canal can have regional nodal spread to the inguinal lymph nodes. These select few patients may remain curable and their radiation fields should include the involved inguinal lymph node basins.
FIGURE 54-4 Lymphatic drainage of the rectum and anus. A. Nodes at the origin of the inferior mesenteric artery. B. Nodes at the origin of sigmoid branches. C. Sacral nodes. D. Internal iliac nodes. E. Inguinal nodes.

**Innervation**

The pelvic autonomic nerves consist of the paired hypogastric (sympathetic), sacral (parasympathetic), and inferior hypogastric nerves (Fig. 54-5).
Sympathetic nerves originate from L1 to L3, form the inferior mesenteric plexus, travel through the superior hypogastric plexus, and descend as the hypogastric nerves to the pelvic plexus. The parasympathetic nerves, or nervi erigentes, arise from S2 to S4 and join the hypogastric nerves anterior and lateral to the rectum to form the pelvic plexus and ultimately the periprostatic plexus. The inferior hypogastric nerve plexus arises from interlacing sympathetic and parasympathetic nerve fibers and forms a fenestrated rhomboid plate on the lateral pelvic sidewall. Fibers from this plexus innervate the rectum as well as the bladder, ureter, prostate, seminal vesicles, membranous urethra, and corpora cavernosa. Therefore, injury to these autonomic nerves can lead to impotence, bladder dysfunction, and loss of normal defecatory mechanisms.

**FIGURE 54-5** Nerve supply of pelvic organs.
Fascial Planes

The walls and floor of the pelvis are covered by the endopelvic, or parietal, fascia (Fig. 54-6). The fascia propria, an extension of the endopelvic fascia, encloses the rectum and its mesorectal fat, lymphatics, and vascular supply as a single unit; forms the lateral stalks of the rectum; and connects to the parietal fascia on the pelvic sidewall. The presacral fascia is the parietal fascia that covers the sacrum and coccyx, presacral plexus, pelvic autonomic nerves, and the middle sacral artery. Posteriorly, a thickening of this fascia, called Waldeyer’s fascia, is the anteroinferior fascial reflection from the presacral fascia at the level of S4. Anteriorly, Denonvilliers’ fascia separates the anterior rectal wall from the prostate and seminal vesicles in the male and is thought to be an entrapped extension of the peritoneum.17
DIAGNOSIS AND EVALUATION

The preoperative evaluation is critically important to treat the cancer optimally and achieve sphincter preservation. With this information, surgeons
must individualize the treatment and care of each patient.

**History**

The patient with rectal cancer usually presents to the surgeon after a definitive endoscopic diagnosis. The patient’s initial complaint may include rectal bleeding, a change in bowel habits or stool caliber, rectal pain, a sense of rectal “fullness,” weight loss, nausea, vomiting, fatigue, or anorexia; however, many patients are completely asymptomatic. Specific symptoms may assist the surgeon in deciding on the optimal approach to therapy. Tenesmus, the constant sensation of needing to move one’s bowels, usually is indicative of a large and possibly fixed stage II or III cancer. Pain with defecation suggests involvement of the anal sphincters; cancers growing directly into the anal sphincter usually are not amenable to sphincter-sparing procedures. Information pertaining to anal sphincter function is invaluable when one is contemplating a low anastomosis. If patients are incontinent, they are better served with an ostomy. Preoperative sexual function is important to know because one must discuss the risks of the procedure and the likelihood of sexual dysfunction postoperatively. Patients who have preexisting sexual dysfunction are at increased risk for worse postoperative function. Diabetics, smokers, and patients who require neoadjuvant radiation are also at increased risk of postoperative sexual dysfunction.

A comprehensive medical history should be aimed at identifying other medical conditions, such as cardiopulmonary, renal, and nutritional issues that may require additional evaluation before surgical intervention. A comprehensive evaluation allows for more accurate risk stratification. Family history or factors predisposing the patient to rectal cancer, such as FAP, HNPCC, MUTYH, and IBD, are important to consider as one plans the operative procedure. For patients with UC/FAP/MUTYH and rectal cancer, the preferred operation is a total proctocolectomy with ileoanal J-pouch reconstruction or end ileostomy, depending on age and sphincter function. One must carefully consider the role of neoadjuvant chemoradiotherapy in patients with rectal cancer and these diseases because once an ileoanal J-pouch is constructed, if radiation has not been given preoperatively, postoperative radiation will severely damage the reconstruction, resulting in poor function and often in the need to remove the J-pouch. In HNPCC, the subsequent lifetime risk of a metachronous cancer is approximately 10% so
either a low anterior resection or APR or total proctoectomy with an ileoanal J-pouch reconstruction can be considered. Whenever an ileoanal J-pouch is created, careful consideration of preoperative radiation is necessary due to the difficulty using radiation on a small bowel reconstruction in the pelvis.

**Physical Examination**

A careful and accurate digital rectal examination (DRE) is critical in determining the clinical stage and any plans for neoadjuvant therapy. Digital exam of a palpable lesion allows for the assessment of tumor size, mobility and fixation, anterior or posterior location, relationship to the sphincter mechanism and top of the anorectal ring, and distance from the anal verge.

Rigid proctoscopy is also essential to the evaluation of patients with rectal cancer because it demonstrates the proximal and distal levels of the mass from anal verge, extent of circumferential involvement, orientation within the lumen, and relationship to the vagina, prostate, or peritoneal reflection. All this information aids in determining the feasibility of local excision if indicated. Rigid proctoscopy also allows one to obtain an adequate tissue biopsy. Flexible sigmoidoscopy is not used routinely because the flexibility of the instrument can give a false distance between the tumor and the dentate line. Furthermore, a mass will often be described as a sigmoid or rectosigmoid tumor on flexible colonoscopy and then when the patient is evaluated in the office with rigid sigmoidoscopy, the lesion is often found to be much lower and in fact is often a true rectal cancer that qualifies for neoadjuvant chemoradiotherapy. Hence, rigid sigmoidoscopy is mandatory for all distal left-sided lesions. A complete colonoscopy to the cecum is essential to rule out synchronous cancers, which occur 2% to 8% of the time. We prefer colonoscopy over virtual colonoscopy so that we may not only diagnose but also excise any amenable polyps. For anterior lesions, women should undergo a complete pelvic examination to determine vaginal invasion.

**Preoperative Staging**

Following the initial history, DRE, and rigid proctoscopy, additional preoperative staging studies can help to determine the appropriate treatment
for each patient, whether radical resection or local excision is warranted, and whether preoperative chemoradiation is recommended. Accurate preoperative staging is gaining increasing importance as combined-modality therapy and sphincter-preserving surgical approaches are considered.

Abdominal and pelvic computed tomography (CT) scans can demonstrate regional tumor extension, lymphatic and distant metastases, and tumor-related complications such as perforation or fistula formation. Its accuracy in determining the depth of invasion, however, is less than that of endorectal ultrasound (ERUS) or specialized magnetic resonance imaging (MRI). Pelvic CT scan therefore is not recommended as the only modality for evaluation of a patient’s primary tumor. For example, the sensitivity of CT scan for detecting distant metastasis is higher (75%-87%) than that for detecting perirectal nodal involvement (45%) or the depth of transmural invasion (70%). If a node is seen on CT scan, it should be presumed to be malignant because benign adenopathy is not normally seen around the rectum.

Intravenous contrast given at the time of a CT scan is important to assess the liver for metastatic disease, as well as to evaluate the size and function of the kidneys. Ureteral involvement by the tumor can be assessed and allows for planning of ureteral stent placement preoperatively. Also, invasion of contiguous structures such as the vagina, prostate, and bladder can be initially evaluated on CT scan. Most importantly, lateral pelvic sidewall invasion must be ascertained as this can be very challenging to resect if the disease burden does not regress substantially with neoadjuvant chemoradiation. All patients should undergo a chest CT scan to exclude pulmonary metastases. Because of newer chemotherapies (Oxaliplatinum, Irinotecan, Avastin, and Cetuximab) and multiple treatment regimens, patients with multiple sites of metastatic disease are more likely to receive chemotherapy alone if the pelvic disease is asymptomatic and/or chemoradiation (symptomatic pelvic disease) followed by chemotherapy and may avoid a surgical resection if they have a large burden of distant disease or multiple sites of metastatic disease.

LABORATORY STUDIES

Complete blood count and electrolytes often are obtained. Liver enzymes may be normal in the setting of small hepatic metastases and are not a reliable marker for liver involvement.

Guidelines published by the American Society for Clinical Oncology
(ASCO) recommend that serum carcinoembryonic antigen (CEA) levels be obtained preoperatively in patients with rectal cancer to aid in staging, surgical treatment planning, and assessment of prognosis. Although neither sensitive nor specific enough to serve as a screening method for the detection of colorectal cancer, preoperative CEA levels greater than 5 ng/mL signify a worse prognosis, stage for stage, than those with lower levels. In addition, elevated preoperative CEA levels that do not normalize following surgical resection imply the presence of persistent disease and the need for further evaluation. CEA is most helpful in identifying recurrent disease with an overall sensitivity rate of 70% to 80%.

ENDOLUMINAL ULTRASOUND

Compared with CT scanning, transrectal endoluminal or endoscopic ultrasound (TRUS) permits a more accurate characterization of the primary tumor and the status of the perirectal lymph nodes. Localized cancers involving only the mucosa and submucosa usually can be distinguished from tumors that penetrate the muscularis propria or extend through the rectal wall into the perirectal fat.

ERUS is an office-based procedure that is well tolerated and can be performed by the surgeon for preoperative planning. Figure 54-7 shows the schematic layers seen in TRUS.

![Schematic of transrectal endoluminal ultrasonography](image)
illustrates the five layers seen on ultrasound.

**T Stage.** Several studies comparing the accuracy of TRUS with CT scan and MRI suggest that TRUS is superior for T staging of rectal cancer. The range of the accuracy of TRUS is 80% to 95% compared with 65% to 75% for CT scan, 75% to 85% for MRI, and 62% for DRE. In one review, the accuracy of TRUS was greatest (95%) in distinguishing whether a tumor was confined to the rectal wall (T1, T2) versus invading into the perirectal fat (T3 or greater) and less able to distinguish accurately T1 from T2 cancers. It is important to understand that all of the above methods are operator dependent; if an institution regularly utilizes ERUS instead of endorectal coil MRI (ecMRI), then that modality will lead to more accurate staging for that institution, and vice-versa if it more regularly utilizes ecMRI. Sometimes, if the lymph nodes are negative and there is a question of whether the tumor is a T2 or T3 lesion, it can be beneficial to get both an ERUS and an ecMRI. Figure 54-8 demonstrates a uT2 lesion. In addition, in patients who have received prior radiation, the accuracy decreases owing to edema and fibrosis.
FIGURE 54-8  Transrectal endoluminal ultrasonography of a uT2 lesion. The arrow indicates the intact serosa.

Despite these data, there is considerable inter-observer variability and a significant learning curve associated with performing TRUS. For these reasons, TRUS under-stages more frequently than over-stages the primary rectal tumor. However, TRUS under-stages the cancer less often than CT scan (15% vs 39%). A modified tumor-node-metastasis (TNM) classification for rectal cancer has been proposed based on TRUS-derived T stage (Table 54-1).
N Stage. TRUS is less useful in predicting the status of perirectal lymph nodes. In several comparative studies, the accuracy of TRUS (70%-75%) was like that of CT scan (55%-65%) and MRI (60%-65%). The accuracy of nodal staging with TRUS requires the nodes to be larger than 5 mm. The contribution of TRUS-guided fine-needle aspiration (FNA) biopsy to N-staging accuracy for rectal cancer is controversial.

MAGNETIC RESONANCE IMAGING

MRI offers some advantages compared with TRUS when it comes to staging rectal cancer. It permits a larger field of view, it may be less operator- and technique-dependent (although it is reader-dependent), and it allows study of stenotic tumors that may not be even amenable to DRE or passage of the ERUS probe. Figure 54-9 illustrates a T3 lesion. Like TRUS, ecMRI or phased-array MRI can discriminate small-volume nodal disease and subtle transmural invasion. These specialized MRI techniques can identify involved perirectal nodes based on characteristics other than size, with reported accuracy rates of up to 95%. Another advantage over TRUS is identification of foci not only within the mesorectum but also outside the mesorectal fascia, such as the pelvic sidewall. We currently prefer phased-array MRI for staging of rectal cancers because it provides equal accuracy in staging compared to ecMRI but without the intrarectal coil.

<table>
<thead>
<tr>
<th>uT1</th>
<th>Invasion confined to the mucosa and submucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>uT2</td>
<td>Penetration of the muscularis propria but not through to the mesorectal fat</td>
</tr>
<tr>
<td>uT3</td>
<td>Invasion into the perirectal fat</td>
</tr>
<tr>
<td>uT4</td>
<td>Invasion into the adjacent organ</td>
</tr>
<tr>
<td>uN0</td>
<td>No enlargement of lymph nodes</td>
</tr>
<tr>
<td>uN1</td>
<td>Perirectal lymph nodes enlarged</td>
</tr>
</tbody>
</table>
**FIGURE 54-9** Endorectal MRI of a T3 lesion. *Arrowhead* indicates the site of the endorectal coil. *Large arrow* demonstrates fingerlike projections of carcinoma invading into the mesorectal fat. *Small arrow* points to the anterior rectal wall. (Used with permission from Koenraad J. Mortele, MD, Beth Israel Deaconess Medical Center, Boston, MA.)

Double-contrast MRI may permit more accurate T staging of rectal cancer by allowing better distinction between normal rectal wall, mucosa, muscularis, and perirectal tissues. In one report, the specificity and sensitivity of ecMRI with combined intravenous and endorectal contrast material to predict infiltration of the anal sphincter were 100% and 90%, respectively. However, N staging was not improved with this approach.

Phased-array surface coil MRI also may be beneficial in predicting the likelihood of a tumor-free resection margin by visualizing tumor involvement of the mesorectal fascia. If confirmed in other series, preoperative MRI may
prove useful in selecting patients at high risk of local recurrence for therapy prior to resection.

**POSITRON EMISSION TOMOGRAPHY**

Fluorine-18 fluorodeoxyglucose–positron emission tomography (FDG-PET) is effective in assessing the extent of pathologic response of primary rectal cancer to preoperative chemoradiation and may predict long-term outcome.\(^{20}\) In addition, it has an accuracy of 87\% for detecting recurrence of rectal cancer after surgical resection and full-dose external-beam radiation therapy.\(^{21}\) While PET scans are positive in 90\% of primary and recurrent tumors and in distant metastatic disease, they are relatively inaccurate for nodal metastases. Rectal cancer rarely metastasizes to the bones or to the brain, and without symptoms these two areas are not included routinely in surveillance imaging. They will, however, light up on PET scan. Current guidelines recommend that PET scans not be used routinely in the standard workup of a rectal cancer.

**TNM STAGING**

The purpose of staging any cancer is to describe the anatomic extent of the lesion. Staging by clinical examination, radiology, and pathology aids in planning treatment, evaluating response to treatment, comparing the results of various treatment regimens, and determining prognosis. Currently, the most widely accepted staging system for rectal cancer in the United States is the TNM classification system.

In 1987, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUC) introduced the TNM staging system for colorectal cancer. The seventh edition was published in 2009 (Tables 54-2 and 54-3). The TNM staging system is based on depth of tumor invasion as well as presence of lymph node or distant metastases. In stage I disease, the tumor may invade into the muscularis propria. In stage II disease, the tumor invades completely through this layer into the perirectal fat (T3) or adjacent organs (T4). Any lymph node metastasis represents stage III disease, and metastatic spread denotes stage IV disease. Depth of invasion (T stage) of the primary tumor is an important prognostic variable as increasing depth of invasion is correlated with an increasing chance of lymph node metastases.
For instance, early-stage cancers extending into the muscularis mucosa (T1) will have up to a 10% to 13% incidence of metastasizing to perirectal lymph nodes.\textsuperscript{22,23} In 805 pathology specimens, Sitzler noted that 5.7% of T1 lesions, 19.6% of T2 lesions, 65.7% of T3 lesions, and 78.8% of T4 lesions had lymph node metastases.\textsuperscript{24}
Primary Tumor (T)
TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis  Carcinoma in situ, intramucosal carcinoma
     (involvement of lamina propria with no extension
     through muscularis mucosae)
T1  Tumor invades the submucosa (through the
     muscularis mucosa but not into the muscularis
     propria)
T2  Tumor invades the muscularis propria
T3  Tumor invades through the muscularis propria into
     pericolectal tissues
T4  Tumor invades the visceral peritoneum or invades
     or adheres to adjacent organ or structure
     T4a Tumor invades through the visceral peritoneum
          (including gross perforation of the bowel through
          tumor and continuous invasion of tumor through
          areas of inflammation to the surface of the visceral
          peritoneum)
     T4b Tumor directly invades or adheres to adjacent
          organs or structure

Regional lymph nodes (N)
NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  One to three regional lymph nodes are positive
     (tumor in lymph nodes measuring ≥0.2 mm), or
     any number of tumor deposits are present and all
     identifiable lymph nodes are negative
     N1a One regional lymph node is positive
     N1b Two or three regional lymph nodes are positive
     N1c No regional lymph nodes are positive, but there are
          tumor deposits in the
          • subserosa
          • mesentery
          • or nonperitonealized pericolic, or perirectal/
            mesorectal tissues.
N2  Four or more regional nodes are positive
     N2a Four to six regional lymph nodes are positive
     N2b Seven or more regional lymph nodes are positive

Distant metastasis (M)
M0  No distant metastasis by imaging, etc.; no evidence
    of tumor in distant sites or organs (This category is
    not assigned by pathologists.)
M1  Metastasis to one or more distant sites or organs or
    peritoneal metastasis is identified
    M1a Metastasis to one site or organ is identified without
          peritoneal metastasis
    M1b Metastasis to two or more sites or organs is
          identified without peritoneal metastasis
    M1c Metastasis to the peritoneal surface is identified
          alone or with other site or organ metastases

Used with the permission of the American College of Surgeons. Amin MB,
Edge SB, Greene FL, et al. (Eds.) AJCC Cancer Staging Manual, 8th Ed. Springer
Generally, the biologic behavior of rectal cancer cannot be predicted by its location or size although there is a consensus among experts that the more distal cancers have a poorer outcome when compared stage for stage with more proximal lesions. Poorly differentiated cancers have a worse long-term prognosis than well or moderately differentiated tumors. Other factors that portend a poor prognosis include direct tumor extension into adjacent structures (T4 lesions), lymph node metastases, lymphatic, vascular, or perineural invasion, and bowel obstruction.

### PRINCIPLES OF TREATMENT
Surgical resection is the cornerstone of curative therapy. Following a potentially curative resection, the 5-year survival rate varies per disease extent (Table 54-4). However, these survival figures may improve with the increased use of adjuvant therapy.

<table>
<thead>
<tr>
<th>TABLE 54-4: SURVIVAL RATES</th>
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<tbody>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
</tbody>
</table>

Surgical and oncologic management varies greatly depending on the stage and location of the tumor within the rectum. Superficially invasive, small cancers may be managed effectively with local excision. However, most patients have more deeply invasive tumors that require major surgery, such as low anterior resection (LAR) or APR. Yet others present with locally advanced tumors adherent to adjoining structures such as the sacrum, pelvic sidewall, vagina, uterus, cervix, prostate, or bladder, requiring an even more extensive operation.

After establishing the diagnosis and completing the staging workup, a decision is made whether to pursue immediate resection or administer preoperative chemoradiotherapy. For patients with stage II and III rectal cancer, the authors advocate for combined preoperative chemoradiotherapy. The authors recommend this for all stage II and III patients with tumors located in the distal two-third of the rectum. For patients with rectal cancer in the proximal one-third of the rectum, the authors use preoperative chemoradiotherapy on a case-by-case basis depending on the size and bulkiness of the tumor and the number of involved lymph nodes as well as the patient’s medical and surgical history.

**Bowel Preparation**

The high bacterial load in the intestinal tract requires preoperative bowel decontamination to reduce the incidence of infectious complications. Prior to
the routine use of mechanical bowel preparation and preoperative antibiotics, the reported rate of infection following colorectal surgery was 60%. A standard bowel preparation includes a clear-liquid diet 24 hours prior to surgery, laxatives and/or enemas, oral antibiotics (erythromycin base and neomycin base) and gastrointestinal tract irrigation with a solution of polyethylene glycol electrolyte lavage (GoLYTELY or Miralax). In two separate surveys of North American colorectal surgeons, almost two-thirds preferred the polyethylene glycol electrolyte solutions because of the reliability of the cleansing results. Certain preparations are contraindicated in patients with certain medical conditions. For example, patients with elevated creatinine or congestive heart failure should avoid the magnesium citrate preparation, whereas patients with gastroparesis should not take a large-volume polyethylene glycol preparation.

Recent studies have shown that mechanical bowel preparation in conjunction with oral antibiotics, a chlorhexidine shower, and a clean closure protocol grouped together as an infection protection bundle have reduced the overall surgical site infection (SSI) rate from 19.7% to 8.2%. The chlorhexidine shower, the oral antibiotics, and the mechanical bowel preparation were all associated with decreased SSI. Moreover, patients who received both oral antibiotics and a mechanical bowel prep had an SSI of 2.7% versus 15.8% for all other patients. Furthermore, a mechanical bowel preparation should be performed in large part because it allows for easier manipulation of the colon and rectum with both open and laparoscopic surgery.

Oral antibiotics are also used to further decrease the incidence of postoperative infectious complications. Although mechanical cleansing decreases the total volume of stool in the colon, it does not affect the concentration of bacteria per milliliter of effluent. The most commonly used regimen is the Nichols/Condon preparation: neomycin 1 g and erythromycin base 1 g, both non-absorbable antibiotics, by mouth at 5:00 pm and 10:00 pm on the day prior to surgery. In addition to oral antibiotics, perioperative systemic antibiotics should be given prior to incision time. A typical choice to cover both aerobic and anaerobic intestinal bacteria is a second- or third-generation cephalosporin in combination with metronidazole. Postoperative antibiotic prophylaxis is not indicated.

Perioperative systemic antibiotic coverage is broadened in patients with
high-risk cardiac lesions such as prosthetic heart valves, previous history of endocarditis, or a surgically constructed systemic-pulmonary shunt, and with intermediate-risk cardiac lesions such as mitral valve prolapse, valvular heart disease, or idiopathic hypertrophic subaortic stenosis. Intravenous ampicillin 2 g and gentamycin 1.5 mg/kg are administered 30 to 60 minutes before the procedure, and ampicillin is repeated once 6 hours postoperatively in place of cefazolin; metronidazole is administered as usual. Vancomycin is substituted for ampicillin if the patient is allergic to penicillin or cephalosporin.

**Enhanced Recovery after Surgery Protocols**

Enhanced recovery after surgery (ERAS) protocols have become popularized in the last several years in colorectal surgery programs across the United States. ERAS protocols have been very successful in decreasing length of stay as well as postoperative surgical complications. These protocols include a preoperative bowel preparation as outlined above while allowing the patient to continue to consume clear liquids up to 2 hours prior to surgery. This aims to limit preoperative dehydration and thereby limit the need for intraoperative fluid administration, which itself leads to third spacing and tissue edema, and as a result, a slower recovery. Patients are also instructed to refrain from taking ACE inhibitors and diuretics the morning of surgery to prevent hypotension and thereby obviate the need for excess intraoperative fluids. In addition to the bowel preparation, a complex carbohydrate load is often given 2 hours prior to the surgery and it is hypothesized that this decreases insulin resistance because it prevents starvation physiology and thereby limits the catabolic effects of starvation generally seen around surgery.

Preoperative pain control is initiated with 1000 mg of Tylenol and a COX-2 inhibitor such as Celebrex and gabapentin (age- and sex-related dosing) in the holding area. Intraoperatively, fluid administration is limited and goal-directed fluid therapy is utilized. Goal-directed fluid therapy is achieved by monitoring urine output (0.25 cc/kg/h) and cardiac stroke volume as monitored with a transesophageal probe. Intraoperative narcotics are minimized. Epidurals and transversus abdominus plane (TAP) blocks and catheters are utilized to further decrease postoperative reliance on narcotics. Exogenous fluid administration is stopped within 6 hours of surgery and patients are immediately started on clear liquids and advanced to regular diet on postoperative day one. This allows for earlier usage and absorption of oral
pain medicines. Liberal use of Tylenol and NSAIDs is recommended as well. ERAS protocols have resulted in a dramatic decrease in length of stay and wound infections, among other complications. An ERAS protocol is an integral part of any program in colon and rectal surgery.

**Goals of Surgery for Rectal Cancer**

The primary goal of surgical treatment for rectal cancer is complete eradication of the primary tumor along with the adjacent mesorectal tissue and the superior hemorrhoidal artery pedicle. Although reestablishment of bowel continuity at the time of surgery has become routine, cancer removal should not be compromised in an attempt to avoid a permanent colostomy.

For tumors located in the extraperitoneal rectum, resection margins are limited by the bony confines of the pelvis and the proximity of the bladder, prostate, and seminal vesicles in men and vagina in women. Although locoregional recurrence may be inevitable, local recurrence, cure, mortality, anastomotic leaks, and colostomy rates after rectal cancer surgery are related to surgical technique as well as to the experience and volume of the individual surgeon and institution.

**Resection Margins**

**DISTAL MARGINS**

The optimal distal resection margin for surgically treated rectal cancer remains controversial. Although the first line of rectal cancer spread is upward along the lymphatics, tumors below the peritoneal reflection can spread distally via intra- or extramural lymphatic and vascular routes.

The use of APR for low rectal cancers traditionally has been based on the need for a 5-cm distal margin of normal tissue. However, in retrospective studies, margins as short as 1 cm have not been associated with an increased risk of local recurrence. Distal intramural spread usually is limited to within 2.0 cm of the tumor unless the lesion is poorly differentiated or widely metastatic. Data from a randomized, prospective trial conducted by the National Surgical Adjuvant Breast and Bowel Project demonstrated no significant differences in survival or local recurrence when comparing distal
rectal margins of less than 2, 2 to 2.9, and greater than 3 cm. Therefore, a 1-to 2-cm distal margin is acceptable for resection of rectal carcinoma, although a 5-cm proximal margin is still recommended.

**RADIAL MARGINS**

The importance of obtaining an adequate circumferential or radial margin has been appreciated more in the last 15 years. In fact, the circumferential radial margin (CRM) is more critical than the proximal or distal margin for local control. Tumor involvement of the circumferential margin has been shown to be an independent predictor of both local recurrence and survival. The Norwegian Rectal Cancer group reported on circumferential resection margins with 29-month median follow-up in 686 patients who had curative intent LAR with TME alone (no adjuvant radiotherapy) for rectal adenocarcinoma. The Norwegian group found that the overall local recurrence rate was 7% (22% with positive CRM and 5% with a negative CRM). Moreover, 40% of patients with a positive CRM developed distant metastases whereas only 12% of those with negative CRM developed distant disease. In this study, a positive CRM clearly affected survival. In another report of 90 patients undergoing resection for rectal cancer, when the radial margins were histologically positive, the hazard ratio (HR) for local recurrence was 12.2, and the HR for death was 3.2 when compared with those with clear circumferential margins. Furthermore, the length of mesorectum beyond the primary tumor that needs to be removed is thought to be 5 cm because tumor implants usually are seen no further than 4 cm from the distal edge of the tumor within the mesorectum. Therefore, in proximal rectal cancers, distal mesorectal excision 5 cm below the lower border of the tumor should be the goal. There is ample evidence, however, that in more distal tumors where there is less mesorectum, a 1- to 2-cm margin is acceptable to achieve sphincter preservation.

**LOCAL EXCISION**

**Oncologic Results**

Several retrospective studies of local excision since the 1970s have
demonstrated a local recurrence rate of 7% to 33% and survival rates of 57% to 87%. Many of these reviews are limited, small, single-institution studies, often combining patients with tumors of different depths, including T3 lesions, positive margins, or those who underwent different forms of local therapy, such as fulguration and snare cautery. Despite these limitations, many of these studies have demonstrated that local excision for superficial tumors with negative margins may provide similar survival and local control but without the morbidity of the APR. Major risk factors for local recurrence include positive surgical margins, transmural extension, lymphovascular invasion, and poorly differentiated/high grade histology. These retrospective studies suggest that local excision of selected distal rectal adenocarcinomas may provide adequate oncologic control at considerably less morbidity than APR.

Several prospective studies have been published (Table 54-5). In a study from the MD Anderson Cancer Center, 46 patients underwent transanal excision of small distal rectal cancer followed by postoperative radiation treatment. Patients with T3 lesions also were given chemotherapy. For patients with negative margins, there was only a 6.5% local recurrence rate (all were T3 tumors) with a 93% overall 3-year survival. Local treatments combined with radiation provided similar oncologic control for T1 or T2 small distal rectal adenocarcinomas as compared with APR.

### TABLE 54-5: RECURRENCE RATES AFTER LOCAL EXCISION AND ADJUVANT THERAPY

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Follow-Up (mo)</th>
<th>Local Recurrence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ota et al.39</td>
<td>46</td>
<td>LE and post-op XRT and 5-FU for T2, T3</td>
<td>36 (median)</td>
<td>6.5% (3/46) All T3s</td>
</tr>
<tr>
<td>Bleday et al.34</td>
<td>48</td>
<td>LE, post-op XRT and 5-FU for T2, T3</td>
<td>41 (mean)</td>
<td>8% (4/48)</td>
</tr>
<tr>
<td>Steele et al.35</td>
<td>110</td>
<td>LE, post-op XRT and 5-FU for T2</td>
<td>48 (mean)</td>
<td>T—5.1% (3/59)</td>
</tr>
<tr>
<td>Greenberg et al.36</td>
<td>110</td>
<td>Same as Steele</td>
<td>85</td>
<td>T2—13.7% (7/51)</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluouracil; LE, local excision; post-op, postoperative; XRT, radiation therapy.

From the New England Deaconess Hospital in Boston, patients with small distal cancers (<4 cm in diameter and <10 cm from the dentate line) with no evidence of metastatic disease were entered in a prospective study. Patients
with T1 lesions were observed after local excision. Patients with T2 lesions treated with local excision were given postoperative chemoradiation. Several patients were found to have T3 lesions and all were recommended further radical surgery. Those who refused had adjuvant chemoradiation therapy and were followed. All patients were followed every 3 months for 2 years and then every 6 months for 5 years. The local recurrence rate in this study was 8%, and the cancer-specific mortality rate was 4%. Risk factors associated with recurrence were T3 cancers or lymphatic invasion. Surgery alone was adequate for T1 lesions, and surgery combined with chemoradiation was appropriate for T2 lesions excised with negative margins. Radical resection was and still is appropriate for tumors with positive margins after local excision or for T3 cancers. Patients with lymphovascular invasion deserve further therapy, although that therapy was not defined.

In his initial report, Steele and colleagues published the only large multicenter prospective trial of local excision (CALGB 8984 [Cancer and Leukemia Group B]). Patients were eligible for the study if their cancer was within 10 cm of the dentate line and was less than 4 cm and involved less than 40% of the luminal circumference. All patients preoperatively were thought to have N0M0 disease, as determined clinically and by CT scan. All study patients had negative margins. T1 lesions had no further treatment, and T2 lesions were treated with chemoradiation. After 6 years of follow-up, the overall survival (OS) and the disease-free survival (DFS) were 85% and 78%, respectively. DFS was 84% and 71% for T1 and T2 lesions, respectively. Seven patients recurred with local disease only and underwent APR with a 70% salvage rate. This approach was no worse than that of radical resection. Longer-term follow-up (median 7.1 years) of CALGB 8984 revealed that 10-year overall survival rates were 84% for T1 lesions and 66% for T2 lesions. DFS was reported at 75% in T1 patients and 64% in those with a T2 lesion. Furthermore, local and distant recurrence rates were 8% and 5% versus 18% and 12% in T1 and T2 lesions, respectively. The longer-term follow-up of CALGB 8984 showed that the rates of local recurrence, OS, and DFS did not change significantly for T1 lesions, but that there was a significant decrease in OS and DFS in the T2 lesions even though these patients received adjuvant therapy. Local excision is indicated for appropriately selected patients and that local excision with adjuvant therapy should be used more judiciously especially in medically fit patients.
Patient Selection and Choice of Operation

Preoperative staging, primarily with ERUS or MRI, is most helpful in identifying appropriate patients for a local excision. Criteria for consideration for local excision are listed in Table 54-6. Patients with T3 or N1 disease are inappropriate for local excision. Given the low probability of microscopic nodal disease in T1 lesions, these patients are the best candidates for local excision. T3 and T4 lesions have a high probability of nodal involvement and therefore should be treated with radical resection. Controversy remains over the best therapy for T2 lesions. Most colorectal surgeons still believe that radical surgery with an LAR or APR remains the standard for T2 lesions. However, local excision combined with postoperative chemoradiation achieves similar rates of survival but not necessarily similar rates of DFS. In patients with a T2 lesion who undergo treatment with local excision and adjuvant chemoradiation, those who have a recurrence ultimately require a salvage APR for cure. The American College of Surgeons Oncology Group (ACOSOG Z6041) was multi-institutional single arm open-label non-randomized trial of patients with T2N0 distal rectal cancer treated with neoadjuvant chemoradiation followed by transanal excision. Preliminary results reported a 44% pathologic complete response rate, 64% pathologic downstaging rate, 5% had ypT3 tumors, and 1% to 2% positive radial margin rate. These preliminary results showed that there was an excellent pathologic complete response and downstaging as well as good surgical outcomes, with nearly all margins being negative.41 Long-term results of this trial were published in 2015. With median follow-up of 56 months the estimated 3-year DFS was 88.2%, suggesting that preoperative chemoradiation followed by local excision is an acceptable alternative to radical surgery, especially when sphincter preservation cannot be offered with radical surgery or when the patient is not medically fit for radical surgery.42

<table>
<thead>
<tr>
<th>TABLE 54-6: CHARACTERISTICS OF TUMORS AMENABLE TO LOCAL EXCISION</th>
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</thead>
<tbody>
<tr>
<td>T1N0 or T2N0 lesion</td>
</tr>
<tr>
<td>&lt;4 cm in diameter</td>
</tr>
<tr>
<td>&lt;40% circumference of the lumen</td>
</tr>
</tbody>
</table>
<10 cm from dentate line
Well- to moderately differentiated histology
No evidence of lymphatic or vascular invasion on biopsy
Patients with extensive metastatic disease and poor prognosis who require local control
Adjuvant treatment for patients with lymphatic invasion, T1 with poor prognosis features, T2 lesions

Tumors less than 3 cm from the dentate line but not invading the sphincters usually can be resected via a transanal procedure. Tumors 5 cm from the dentate line may need a transcoccygeal approach or transanal endoscopic microsurgery (TEM). Tumors 7 to 10 cm from the dentate line require TEM or should be considered for an LAR. Clearly, tumors tethered to the mesorectum or pelvic floor on physical examination, suggesting transmural involvement, are not amenable to local excision. Patients with such lesions should undergo preoperative radiation followed by a radical resection.

Patients considered medically unfit for a major resection are good candidates for local treatment of most small, mobile tumors, including T2 and T3 lesions, accepting a higher rate of local recurrence. In these circumstances, adjuvant chemoradiation is advocated, and close follow-up is mandatory.

After local excision, if the pathology is unfavorable, the patient should be counseled to have further therapy, including chemoradiation therapy and either an LAR or APR with TME. Local excision in these circumstances can be considered an open biopsy and not the definitive therapy.

**Technique**

There are four approaches to local excision: transsphincteric, transanal, transcoccygeal, and TEM. The transsphincteric technique, however, leads to significant dysfunction of the anal sphincters with subsequent moderate to severe fecal incontinence. Therefore, the transanal, transcoccygeal, and TEM approaches are the preferred techniques.
Transanal Excision

Most small distal rectal cancers can be excised locally via a transanal excision. Tumors amenable to this approach usually range from 6 to 8 cm above the anal verge, which is the same as 3 to 4 cm above the anorectal ring.

Prior to the procedure, all patients should receive a full mechanical and antibiotic bowel preparation. Most patients are placed in the prone jackknife position, and the buttocks are taped apart. For lesions that are directly posterior, the lithotomy position can be used. The surgeon wears a fiberoptic headlight. A pudendal nerve block using 0.5% Marcaine (bupivacaine) with 1:100,000 units of epinephrine is administered to relax the sphincters and facilitate postoperative pain control. A Lone Star retractor (Cooper Surgical, Inc., Trumbull, CT) can be used to expose the dentate line. A Pratt bivalve retractor (Pilling-Weck Instruments, Ft. Washington, PA), a Fansler operating speculum (Hayden Medical, Inc., Santa Clarita, CA) or Parks anal retractor (CS Surgical, Inc., Slidell, LA) should be inserted to dilate the anus and expose the lesion. Once the tumor is viewed adequately, traction sutures using 2-0 Vicryl (Ethicon, Somerville, NJ) are placed 2 cm proximal to the tumor. The circumferential dissection line is outlined on the mucosa using the cautery with a pinpoint Bovie tip approximately 1 cm from the border of the tumor; careful attention should be paid to maintaining a wide proximal margin. If an adequate view of the lesion cannot be obtained initially, serial traction sutures starting distally are used to prolapse the lesion into the field. Additional local anesthetic is injected submucosally circumferentially along the Bovie markings to provide hemostasis. Starting proximally and proceeding circumferentially, a full-thickness incision of bowel wall is made down to perirectal fat using the cautery along the previously marked mucosa (Fig. 54-10). Once fat is reached, the dissection is made through the fat to undercut the specimen. Anteriorly in a female patient, one must not injure the posterior wall of the vagina. In a male patient, one must avoid the prostate. Once the specimen is free, carefully maintain and mark the orientation for the pathologist (eg, proximal, anterior, left, right). Irrigate and check for hemostasis. After excision, the defect in the bowel wall is closed transversely with full-thickness bites using interrupted 2-0 Vicryl sutures on a UR-6 needle. One stitch is placed in the center of the incision. One-half is closed, followed by the other. A rigid sigmoidoscope is inserted to visualize the suture line and to ensure patency of the rectal lumen. The patient then is
placed supine. A pad is applied to the rectal area and secured with mesh rectal shorts. A pack in the anal canal or rectum is not used. These procedures can be done either as an outpatient or with a 23-hour observation status. Potential complications include urinary retention, urinary tract infections, fecal impaction, infections in the perirectal and ischiorectal spaces, and delayed hemorrhage. The incidence of these complications is quite low; mortality in most series is zero.

**FIGURE 54-10** Approach to transanal excision of a rectal tumor. **A.** A 1- to 2-cm margin is marked circumferentially with Bovie electrocautery on the rectal mucosa. **B.** Full-thickness excision down to perirectal fat is performed. **C.** The specimen is oriented for the pathologist. (Reproduced with permission from Bleday R: Local excision of rectal cancer, *World J Surg* 1997:Sept;21(7):706-714.)
Transcoccygeal Excision

Originally popularized by Kraske, the transcoccygeal excision is used for larger or more proximal lesions within the middle or distal third of the rectum. Bleday et al. reported that the average distance of the distal margin of an appropriate tumor that was selected for the posterior or Kraske approach was approximately 4.8 cm from the dentate line. This approach is useful for lesions on the posterior wall of the rectum but can be used for anterior lesions.

Patients undergo similar bowel preparation and thrombosis precautions as the transanal excision patients. The patient is placed in the prone jackknife position. The buttocks are taped apart for better exposure, but at closure the tape is released to facilitate approximation of the subcutaneous tissues and skin. After prepping the skin, the rectum is irrigated with a Betadine (povidone/iodine) solution. The incision is made in the intergluteal fold over the sacrum and coccyx down to the upper border of the posterior aspect of the external sphincter. After division of the skin and subcutaneous tissues, one encounters the coccyx and anal coccygeal ligament. To obtain optimal exposure, the coccyx is removed by cauterizing its attachments, including the anal coccygeal ligament, from each side and from its lower edge and then proceeding with the dissection on its undersurface. A cutting wire is used to transect the sacral coccygeal joint. With removal of the coccyx, bleeding from an extension of the middle sacral artery is controlled with electrocautery. The levator ani muscles are separated in the midline, exposing a membrane that is just outside the mesorectal fat. Once this membrane is divided, the rectum can be completely mobilized within the intraperitoneal pelvis. For anterior lesions, a posterior proctotomy is made; the anterior rectum is approached under direct vision, with removal of the tumor along with a 1-cm margin (Fig. 54-11). For posterior-based lesions, after complete mobilization of the mesorectum, the distal margin of the tumor can be palpated via a rectal examination; the mesorectum and rectum are transected approximately 1 cm distal to the tumor (Fig. 54-12). The tumor is excised with a 1-cm margin of normal tissue. The advantage of the posterior approach is that the immediate mesorectal tissue adjacent to the tumor is removed along with perirectal nodes. After removal, the specimen is oriented for the pathologist. The incision is closed in a transverse manner using an absorbable suture such as 3-0 Vicryl or 3-0 PDS (Ethicon, Somerville, NJ). After closure
of the rectum, an air test is performed by insufflating the rectum with air and filling the operative field with sterile saline. After all air leaks are controlled, the levator ani musculature is reapproximated and the anal coccygeal ligament is reattached to the sacrum, followed by closure of the subcutaneous tissues and skin.

**FIGURE 54-11** Kraske approach to an anterior lesion. The coccyx is excised, the levator is split in the midline, and the rectum is mobilized. The posterior rectal wall is opened to expose an anterior lesion. (Reproduced with permission from Bleday R: Local excision of rectal cancer, *World J Surg* 1997:Sept;21(7):706-714.)
FIGURE 54-12  Kraske approach to a posterior lesion. After the rectum has been exposed, the surgeon may palpate the distal margin of the tumor. The tumor is excised with a 1-cm margin. (Reproduced with permission from Bleday R: Local excision of rectal cancer, World J Surg 1997:Sept;21(7):706–714.)

One of the most troubling complications of the transcoccygeal excision is a fecal fistula extending from the rectum to the posterior incision. The incidence of this complication ranges from 5% to 20%.39 These fistulas usually heal after temporary fecal diversion.

**Transanal Endoscopic Microsurgery**
The TEM technique was first described by Gerhard Buess of Tubingen, Germany, in 1980. It is especially useful for small benign and malignant lesions in the mid and proximal rectum that are too high for a traditional transanal excision. This technique is widely used in Europe but over the years has been underutilized in North America until recently. It is gradually becoming standard practice for early mid to upper rectal lesions. The specialized instrumentation includes a 4-cm Wolf operating proctoscope (Richard Wolf Company, Frankfurt am Main, Germany) in lengths of 12 and 20 cm with a flat or beveled end. The operating proctoscope is equipped with a binocular microscope and videoscope attachment for viewing on a standard laparoscopy tower. A CO$_2$ insufflator and long operating surgical instruments are needed as well. The surgeon must be trained in the technique, which follows the same principles as transanal excision described earlier using the pinpoint tip on the Bovie electrocautery. Preoperative localization in the office with a rigid sigmoidoscope is essential so that the patient can be appropriately positioned. The patient is positioned using a beanbag and fixation to the table with tape, which allows the patient to be rotated laterally during the procedure. For an anterior lesion, the patient is placed in the prone jackknife position. For a posterior lesion, the patient is placed in a modified lithotomy position. For lateral lesions, the patient can be placed on the appropriate side so that the lesion is at the inferior quadrant of the visual field. After the patient is appropriately positioned, the operating proctoscope is fixed to the table with a rigid support arm and a glass faceplate. The faceplate is equipped with two operating ports and a suction port. The rectum is distended with carbon dioxide anywhere from 15- to 26-cm water pressure so that the tumor can be visualized and the resection and closure of the rectum can be completed. After full-thickness excision of the lesion is completed, the defect is endoscopically closed with interrupted 3-0 PDS figure-of-eight sutures. If this cannot be performed, the defect may be left open as in a standard transanal excision. The one caveat, however, is that extreme care must be taken to identify the peritoneal reflection, especially anteriorly. If dissection carries into the peritoneal cavity, the defect must be closed. If we enter the peritoneal cavity, after we close the defect our practice is to observe these patients in hospital until they are passing flatus. In selected patients, temporary diversion is needed after entering the peritoneal cavity. Patients in whom TEM is contemplated should be made aware that because of technical considerations (proctoscope won’t fit or pass and/or
poor visualization or entry into the peritoneal cavity), an LAR may need to be performed. This is especially true in patients with a known malignancy.

Unfortunately, the literature describing oncologic outcomes for TEM resection of early-stage rectal adenocarcinoma is mainly single-institution, small-series, with short-term follow-up. Most of these studies make a comparison with radical surgery (LAR, APR) but never make a direct comparison with transanal resection. For the most part, the comparison of TEM to traditional transanal excision is made with historical data alone. This is in part because very distal lesions near the sphincter are difficult to excise with the TEM and a traditional transanal excision is easier, whereas the more proximal lesions are not amenable to a traditional approach and a TEM is more likely to succeed in removing these lesions per rectum. Hence only a small number of tumors that are above 8 cm and below 10 cm from the anal verge could ever be enrolled in a trial to make a direct comparison. To address this issue, a multicenter randomized trial comparing TEM to traditional transanal excision for early-stage rectal cancer with and without adjuvant radiotherapy needs to be performed. To date such a trial has not been done.

TEM resection of low-risk T1 rectal adenocarcinoma results in a 0% to 11% local recurrence rate, whereas local recurrence for T2 lesions without adjuvant therapy is approximately 19% to 35%. When T2 and T3 lesions are treated with adjuvant or neoadjuvant therapy and TEM resection, the local recurrence rates decrease to 14% and 3%, respectively. One caveat is that these studies have short-term follow-up, with the longest being 4 years. Indirect comparisons of local excision with TEM for T1 lesions have similar local recurrence rates (7%-18% transcatheter arterial embolization [TAE] vs 0%-11% TEM), and thus the decision to perform traditional transanal excision versus TEM should depend on the location of the tumor and the individual surgeon’s expertise. Local recurrence rates without chemoradiotherapy for either TEM or transanal excision, on the other hand, are not satisfactory. Local recurrence rates for T2 lesions excised by TEM range from 19% to 35% versus 26% to 47% for traditional transanal excision (see Table 54-5). In either case, the results are not adequate, and as a result, medically fit patients with T2 lesions should not have either a TEM or a transanal excision without the addition of radiotherapy.

In summary, the results of TEM resection are as good as or better than traditional transanal resection for early rectal cancer. When deciding whether
to utilize transanal excision or TEM, the surgeon should remember that TEM offers better visualization, almost complete intact excision, and access to lesions that are higher in the rectum and otherwise would need radical surgery. Cataldo’s group from the University of Vermont has shown that TEM resection resulted in intact nonfragmented excision 94% of the time, whereas transanal excision only accomplished intact nonfragmented excision 65% of the time \( (p < .001) \) and tumor-free margins were 98% with TEM versus 78% with TAE when resecting a rectal cancer \( (p = .03) \). Furthermore, they showed a nonstatistically significant trend to lower recurrence rates \( (22\% \text{ for TAE and } 3\% \text{ for TEM}) \).\(^{43}\)

**LOW ANTERIOR RESECTION WITH TOTAL MESORECTAL EXCISION**

**Oncologic Results**

Local failures most often result from inadequate surgical clearance of the radial margin. The concept of TME proposed by Heald et al. has been shown to improve both disease-free and overall survival.\(^4\) TME in conjunction with an LAR or APR involves precise dissection and removal of the entire rectal mesentery, including that distal to the tumor, as an intact unit. Unlike conventional blunt dissection, which may leave residual mesorectum in the pelvis, TME involves sharp dissection under direct vision in the avascular, areolar plane between the fascia propria of the rectum, which encompasses the mesorectum, and the parietal fascia overlying the pelvic wall structures. This procedure emphasizes autonomic nerve preservation (ANP) and complete hemostasis and avoids violation of the mesorectal envelope. This results in a characteristic bilobed, smooth, glistening surface of the excised mesorectum.

Because rectal cancer spread appears to be limited to the mesorectal envelope, its total removal should encompass virtually every tumor satellite, thus improving the likelihood of local control. The excellent results with TME may be attributed to improved lateral clearance with removal of potential tumor deposits in the mesentery and decreased risk of tumor spillage from a disrupted mesentery.\(^44\) The completeness of the mesorectal
excision influences local control, even if the surgical margins are uninvolved. In one report, both local (11.4% vs 5.5%) and distant recurrence rates (19.2% vs 12.2%) were higher in patients with an incomplete, as compared with a complete or nearly complete, mesorectal resection. These favorable results have led some to question the need for routine postoperative radiation in patients undergoing complete resection of rectal cancer with TME. However, the Dutch neoadjuvant trial that randomly assigned 1861 patients with resectable rectal cancer to TME alone or a short course of preoperative radiation (5 Gy daily for 5 days, in the “Swedish style”) followed by TME demonstrated a significantly decreased rate of local recurrence 8.2% versus 2.4% at 2 years.45

Of greatest importance is that improved local control appears to result in better overall survival. In one of the earliest reports, Heald et al. noted a local recurrence rate of 3.6% and a survival rate of 86% after 9 years of follow-up.46 In 1994, the Norwegian Rectal Cancer Group was founded to improve the surgical standard by implementing TME on a national level and to evaluate the results; courses were arranged to teach surgeons the technique of TME. Optimized TME reduced the rate of local recurrence (6% TME vs 12% non-TME) and increased overall survival (73% TME vs 60% non-TME) within 2 years.47 This led to a strategic change in both Norway and the United States to initiate quality assessment in the surgical treatment of rectal cancer.

Guillem et al. recently demonstrated an improved overall and disease-free survival in patients with T3 or N1 tumors who underwent TME after preoperative combined-modality therapy.48 With a median follow-up of 44 months, the estimated 10-year overall survival was 58% (Fig. 54-13), and 10-year recurrence-free survival was 62% (Fig. 54-14). On multivariate analysis, pathologic response greater than 95%, lack of lymphovascular invasion and/or perineural invasion (PNI), and lack of postoperative positive lymph nodes were significantly associated with improved overall and disease-free survival.

FIGURE 54-14 Five- and ten-year recurrence-free survival with 95% confidence intervals of rectal cancer patients following preoperative

**Lateral Nodal Dissection**

Despite the advent of TME and the addition of neoadjuvant chemoradiotherapy to the treatment of patients with rectal cancer, there is still a risk of local pelvic recurrence and the appearance of distant metastatic disease. Lateral nodal spread, especially in distal rectal cancers, is one possible culprit for treatment failures in rectal cancer. It is well established that distal rectal adenocarcinomas have a worse prognosis than more proximally based lesions. Most surgeons attribute this to three factors: (1) distal tumors require a more difficult low dissection in a narrow pelvis; (2) there are probably biologic differences in tumors with the low-lying tumors possibly having a poorer biology; and (3) the more distal tumors have a predilection to more complex lymphatic channels and the possibility of lateral spread into the systemic circulation as well as the portal circulation.

Takahashi et al. performed a retrospective analysis of 764 patients over a 20-year period (1975-1995) who underwent a curative three-space dissection. The three spaces are defined as: (1) the inner space, which is encircled by the visceral pelvic fascia posteriorly and Denonvilliers’ fascia anteriorly, and laterally the three spaces unite near the pelvic nerve plexus; (2) the intermediate space, which is defined by the parietal pelvic fascia posteriorly and the internal iliac arteries and branches laterally and anteriorly; and (3) the outer space, which is lateral to the internal iliac arteries. Takahashi found that 66 of 764 patients (8.6%) had lateral nodal spread of their rectal cancer. More importantly, 16.4% of the low-lying rectal cancers had their lower margins less than 5 cm above the dentate line. Lateral nodal spread is outside the traditional TME resection plane but can be encompassed by a three-space lateral nodal dissection in appropriate patients. When this was achieved, they had a 42.4% 5-year survival in their subgroup of patients who had lateral spread and a curative three-space dissection.49

A comparative study of Japanese and Dutch patients examined local recurrence in Dutch patients who received TME alone versus TME plus preoperative radiotherapy and Japanese patients who were treated with TME.
plus lateral nodal dissection (LAR or APR). Most Japanese patients did not receive neoadjuvant therapy. Local recurrence, lateral pelvic recurrence, and presacral recurrence rates were analyzed and are shown in Table 54-7.

**TABLE 54-7: ANALYSIS OF LOCAL, LATERAL PELVIC, AND PRESACRAL RECURRENCE RATES**

<table>
<thead>
<tr>
<th></th>
<th>TME Alone (%)</th>
<th>TME + RT (%)</th>
<th>TME + Lateral Dissection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>12.1</td>
<td>5.8</td>
<td>6.9</td>
</tr>
<tr>
<td>Lateral pelvic</td>
<td>2.7</td>
<td>0.8</td>
<td>2.2</td>
</tr>
<tr>
<td>recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presacral</td>
<td>3.2</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>recurrence</td>
<td></td>
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In summary, both TME with radiotherapy and lateral nodal dissection without radiotherapy result in excellent local control and have improved local control over TME alone. The conclusion is that the radiotherapy sterilizes the lateral space that has microscopic tumor extension beyond the traditional TME resection plane. The major caveat is that patients who have TME alone have much better postoperative sexual and urinary function than those who have TME plus lateral nodal dissection.

**Quality of Life**

Quality of life has improved with TME and ANP. Conventional rectal surgery is associated with a significant incidence of impotence, retrograde ejaculation, and urinary incontinence/retention, presumably owing to damage to the pelvic autonomic parasympathetic and sympathetic nerves by blunt dissection. Postoperative impotence, retrograde ejaculation, or both are observed in 25% to 75% of conventionally treated patients compared with only 10% to 29% of patients after TME with its careful nerve-sparing dissection.

Erectile capacity and normal ejaculation may be preserved in most male patients, especially those 60 years of age or younger. In one retrospective
study of patients undergoing TME with ANP, 86% of male patients younger than 60 years and 67% of those 60 years or older were able both to engage in postoperative sexual intercourse and to achieve orgasm.\textsuperscript{52} In female patients, sexual activity was maintained in 86%, sexual arousal with vaginal lubrication in 98%, and the ability to achieve orgasm in 91%. With the advent of pelvic dissections that preserve autonomic nerves, postoperative sexual dysfunction rates have been reduced from greater than 50% to 10% to 28%.\textsuperscript{52}

Isolated urinary dysfunction is uncommon with preservation of the pelvic autonomic nerves. In a prospective study of rectal cancer patients undergoing TME with ANP, only 2 of 35 had difficulty with bladder emptying and possessed evidence of bladder denervation on postoperative studies.\textsuperscript{52}

Some studies, however, have demonstrated impaired quality of life owing to LAR with TME in part because of a temporary loop ileostomy or preoperative radiotherapy. However, cost-utility analysis estimates that improved survival outweighs impaired quality of life.\textsuperscript{53}

**Technique of Total Mesorectal Excision**

Prior to the procedure, all patients receive a full mechanical and antibiotic bowel preparation. The patient’s abdomen is marked preoperatively by the enterostomal therapy nurse for potential stoma sites. An epidural catheter is placed by the anesthesia team for postoperative pain control. Sequential compression devices are applied to the lower extremities before general anesthesia is induced for deep vein thrombosis (DVT) prophylaxis. One dose of 5000 units of heparin is administered subcutaneously. A second- or third-generation cephalosporin and metronidazole are infused. After anesthesia is induced, the patient is brought down on the table so that the buttocks are at the edge; a gel pad placed under the buttocks facilitates access to the anus. The patient is placed in a modified lithotomy position using Allen or Yellow Fin stirrups (Fig. 54-15). The hips are minimally flexed and abducted. The feet are positioned flat in the stirrups; an imaginary line is visualized keeping the ankle, knee, and contralateral shoulder in a straight line. Care is paid to having no pressure on the peroneal nerve or bony prominences; a hand should be able to be placed easily between the posterolateral aspect of each lower leg and its respective stirrup. If the patient has had previous pelvic surgery or evidence of hydronephrosis on CT scan, consider bilateral ureteral
stent placement. A Foley catheter is placed and is draped over one leg. A nasogastric tube is inserted by the anesthesia team. A DRE is performed. If there is any question regarding the distal or proximal limits of the tumor, rigid proctoscopy may be performed now. Preoperatively, the lesion may have been marked by an injection of India ink. The surgeon should wear a headlight to help with visualization in the lower pelvis. Most surgeons stand on the patient’s left, which allows them to operate more efficiently with their right hand in the lower pelvis. A low midline incision is made between the umbilicus and the pubis, keeping in mind potential stoma sites; cephalad extension may be necessary to mobilize the splenic flexure. The abdomen is explored to search for metastatic disease in the liver, pelvic organs (ovaries), or peritoneal surfaces. The rectum is palpated to assess the primary mass. The colon is palpated for any synchronous lesions. A wound protector is then placed and a self-retaining tractor may also be used.
FIGURE 54-15 Position of patient for surgical treatment of rectal cancer allows access to both the abdomen and the perineum.

The abdominal self-retractor is set up. The patient is placed in slight Trendelenburg position. The sigmoid colon is mobilized laterally by scoring the white line of Toldt (Fig. 54-16A). The left ureter may be identified by several methods: visualizing it cross over the bifurcation of the common iliac artery, palpating the external iliac artery and pinching the tissue above it, locating it at the level where the sigmoid turns, or incising the peritoneum over the psoas muscle and finding the ureter on the medial aspect of the peritoneum (Fig. 54-16B). In general, the left ureter is found deep and medial to the gonadal vessels. After mobilization of the sigmoid colon and identification of the left ureter, the surgeon should ascertain if much length will be necessary for reconstruction of the rectum. If additional conduit is needed for the reconstruction, then the splenic flexure is mobilized. Tension on the colon should be gentle but firm; too much traction on the colon or omentum can cause splenic injury. The transverse colon is freed from the omentum by sharp dissection along the avascular plane between the two structures. The bowel is packed into the upper abdomen. The sigmoid is held up in the air at the junction between the descending colon and sigmoid. Both sides of the mesentery are scored from this point down to the sacral promontory. The right ureter is identified. The colon usually is divided proximal to the rectosigmoid junction using a linear stapler (or may be divided between two bowel clamps, which would require a hand-sewn anastomosis). The sigmoidal vessels are isolated and divided. The vessels are doubly ligated. The colon is packed cephalad, out of the field. The superior hemorrhoidal artery is then divided at the junction with the left colic artery (Fig. 54-16C). A more proximal ligation of the inferior mesenteric vessel can also be performed if extra length on the colon is needed, but it is not necessary to ligate the IMA flush with the aorta for oncologic reasons. One usually suture-ligates the superior hemorrhoidal vessels to ensure hemostasis. If additional length is still required, then division of the inferior mesenteric vein near the root of the transverse mesocolon just lateral to the fourth portion of the duodenum will give additional length.
FIGURE 54-16 Mobilization of the left colon. A. Incision line around the left colon. B. Left colon reflected medially, exposing the ureter and gonadal vessels. C. Superior hemorrhoidal artery is divided close to the aorta to result in a high arterial ligation. The arcade of Riolan is preserved, and the left colon and mesentery are divided at the junction of the descending and sigmoid colon. D. Proximal ligation of the inferior mesenteric vein adds extra mobility.
After dividing the superior hemorrhoidal artery, it is important to find the proper plane of dissection at the sacral promontory. One first locates the sympathetic nerves along the pelvic brim. The rectum is retracted anteriorly. Electrocautery with a long Bovie tip is used to develop the loose areolar plane of avascular issue posteriorly (Fig. 54-17B). The nerves are visualized and kept posterior and lateral to the plane of resection. The presacral fascia is incised down to Waldeyer’s fascia, and the dissection is carried inferiorly to the tip of the coccyx. The St. Mark’s abdominal retractor facilitates the deep pelvic dissection.
FIGURE 54-17 Mobilization of the rectum. A. Peritoneal incision of the pelvis. B. Rectum reflected anteriorly and posterior avascular plane entered between the presacral fascia of Waldeyer and the fascia propria of the rectum. C. Division of lateral stalks. D. Projected line of dissection in pelvis through Waldeyer’s and Denonvilliers’ fascia.

The anterior and lateral dissections are then started after the posterior dissection has been partially completed. The peritoneum is incised on each side and then across the anterior midline at the deepest point in the cul-de-sac. The anterior peritoneum is incised in the groove between the rectum and the anterior structures (uterus/vagina in women, seminal vesicles/prostate in men) (Fig. 54-17A). The mesorectum is separated from the pelvic sidewall using the cautery to divide the thin areolar tissue that is found when one is dissecting in the proper plane. The dissection is carried down anterolaterally to the lateral ligaments or “stalks” (Fig. 54-17C). Only 25% of patients have distinct branches of the middle rectal vessels in these ligaments. They can be divided flush with the pelvic sidewall, but care should be taken to preserve the hypogastric plexus that lies on the pelvic sidewall just lateral to the seminal vesicles in men or just lateral to the cardinal ligaments in women. Preservation of the plexus helps with avoiding postoperative erectile dysfunction or urinary problems, and resection of the plexus is rarely helpful for oncologic reasons. Throughout the lateral dissection, one should be aware of the nerves and vessels along the pelvic sidewall. Too lateral a dissection can cause bleeding from the pelvic sidewall.

Anteriorly, the planes are less distinct, and the fat of the mesorectum is thin. The vaginal wall or seminal vesicles are elevated anteriorly using the lipped St. Mark’s retractor while the surgeon places posterior traction on the rectum. In the male patient, the dissection is continued through or anterior to Denonvilliers’ fascia (Fig. 54-17D). This fascia is often two layers of a thin membrane. When performing a cancer resection, one should take both layers of this membranous fascia off the seminal vesicles and upper prostate if possible.

POINT OF TRANSECTION
For middle to low rectal cancers, TME involves removing the entire mesorectum with its enveloping fascia as an intact unit. For tumors in the
upper rectum (>10 cm from the anal verge), TME is extended to 5 to 6 cm below the level of the tumor, dividing the rectum and mesorectum at the same level. Several pathologic studies demonstrate that tumor spread within the mesorectum rarely extends beyond 4 cm distal to the caudal edge of the tumor; usually most nodes or mesorectal implants are within 3 cm of the distal edge of the tumor. However, multiple studies have shown that a 1- to 2-cm margin is adequate on the mucosa. Fewer than 2% to 4% of tumors will have mucosal or submucosal spread beyond 2 cm distally. Rigid sigmoidoscopy may be used to identify the appropriate site for transection if the cancer is not palpable, especially after neoadjuvant therapy.

Once the rectum has been mobilized, a tumor measured at 5 cm by rigid proctoscopy often may be moved to 8 cm from the dentate line, a distance that permits an adequate resection margin and sphincter preservation (Fig. 54-18).

FIGURE 54-18 Tumor position relative to the dentate line after mobilization
of the rectum. This may permit a sphincter-preserving resection.

When the distal extent of the tumor and the site of transection have been established, electrocautery is used to dissect the mesorectal fat away from the rectum. Vessels require ligation with 2-0 Vicryl ties or an energy device such as the LigaSure (Valleylab: Boulder, CO). It is important to keep the dissection of the mesorectum perpendicular to the site of transection. “Coning in” as one divides the mesorectum prior to transection should be avoided.

Once the bowel has been cleared of mesorectal fat, a 30-, 45-, or 60-mm TA linear stapler or a curved 40-mm contour stapler (Ethicon, USA) is used to staple the rectum (Fig. 54-19A). This is the first staple line in the “double-stapling technique.” The contour stapler staples on either side and divides between, whereas the linear TA staplers require that the specimen side of the bowel is clamped just proximal to this linear stapler. A no. 10 blade on a long handle is used to transect the bowel. The specimen is handed off the field.
**FIGURE 54-19** Colorectal anastomosis: double-staple technique. **A.** Transection of the distal rectum with a linear stapler. **B.** Stapling instrument introduced through rectum. **C.** Descending colon purse-string suture is tied around shaft of anvil. After the trocar of the circular stapler penetrates behind the staple line, the trocar is removed before reconnecting the anvil to the shaft. **D.** The circular stapler is reconnected, reapproximated, and fired. **E.** The anastomosis is complete. **F.** The proximal and distal staple lines are examined for intact inner “donuts.”

**RECONSTRUCTION: DOUBLE-STAPLING TECHNIQUE**

The proximal colon is unpacked, and the length required for a tension-free anastomosis is determined. If more colon is needed, the splenic flexure is mobilized further. This may require an extension of the incision cephalad. Proximal ligation of the inferior mesenteric vein also adds extra mobility (see Fig. 54-16D). The proximal bowel is cleaned by resecting residual fat and small vessels approximately 1 cm proximal to the staple line. The staple line is excised with Bovie electrocautery. We routinely use a 28-mm end-to-end anastomosis (EEA) circular stapler. The anvil is placed within the opened bowel and a 3-0 Prolene is used to take full-thickness, 1- to 2-mm bites to fashion a purse-string stitch around the anvil. The purse-string suture is tied gently but firmly around the shaft so that the shaft is completely encircled by bowel (Fig. 54-19C). If there are any gaps, an additional 3-0 Prolene suture can be used to take another full-thickness bite, and this suture may be tied around the shaft as well. The serosa of the bowel is cleaned further of fat and small vessels within 1 cm of the shaft of the anvil to optimize bowel-to-bowel contact when the circular stapler is applied. One can also perform a similar placement of the anvil on the antimesenteric side of the colon for a side-to-end anastomosis. The optimal placement of the anvil in this case is such that only a small blind end of colon remains distal to the anastomosis (1-5 cm).

Attention then is turned to the pelvis, which is irrigated and inspected for hemostasis. This is truly the last opportunity to inspect this area because exposure will be compromised once the anastomosis is completed.

One member of the team then stands between the patient’s legs. The circular stapler is coated with lubricant on the outside of the stapler; we do not place lubricant on the staples themselves. The tip is retracted fully. A rectal examination is performed, and the anus is dilated gently with two to
three fingers to accommodate the stapler. The circular stapler is inserted gently following the curve of the sacrum—initially straight in and then the stapler is tilted posteriorly. Using close communication with the surgeon overlooking the abdomen, the assistant positions the circular stapler tip so that the trocar will exit either 2 to 3 mm anterior or posterior (we elect to do this posteriorly in women to avoid the vaginal wall) to the staple line (Fig. 54-19B). The trocar then is advanced slowly; the bowel continues to be adjusted as necessary. When the spiked trocar protrudes through the bowel wall, be sure that the trocar is fully advanced so that its bottom is visualized (see Fig. 54-19C). The surgeon controlling the proximal bowel should at this point ensure that the proximal bowel is not twisted and that the remaining bowel, mesentery, and epiploicae are held away. The anvil is then brought down gently to the stapler and connected to the spiked trocar. The colon is inspected again to verify that no adjacent tissue is entrapped. The stapler is closed slowly until both pieces of colon are fully approximated (Fig. 54-19D). The stapler is fired, opened slightly, and gently removed. This is the second staple line in the double-stapling technique (Fig. 54-19E). The stapler is opened, and the tissues from the proximal and distal bowel are inspected to make sure that the two rings of tissue, or “donuts,” are intact (Fig. 54-19F). If they are not intact, additional sutures are placed if a visible gap is apparent. All anastomoses are checked for integrity. The surgeon fills the pelvis with saline and clamps the bowel proximal to the anastomosis gently with the index and third finger in a scissor fashion. At this point the assistant between the legs introduces a rigid sigmoidoscope into the rectum and insufflates air. If bubbles cannot be detected, one can be confident that the anastomosis is intact. If bubbles are detected, additional sutures are placed in suspected areas, and a diverting loop ileostomy is constructed. If the anastomosis is disrupted completely, it must be refashioned.

**DIVERTING LOOP ILEOSTOMY**

A diverting loop ileostomy should be considered in any low anastomoses (<5 cm) from the dentate line as these anastomoses are associated with anastomotic leak rates of up to 17%. Other risk factors for anastomotic breakdown include a history of radiation, perioperative steroid use, malnutrition, elderly women with a thin rectovaginal septum, or elderly patients undergoing preoperative combined-modality therapy with planned
postoperative chemotherapy. Additionally, if there is any question regarding the integrity of the anastomosis, an ileostomy should be created.

Ileostomies can be closed within 8 weeks but often are left in place until the patient completes adjuvant chemotherapy. A Gastrograffin (diatrizoate meglumine) enema is used to check the patency and integrity of the anastomosis prior to ileostomy reversal.

**DRAIN PLACEMENT**

Most surgeons continue to advocate routine use of drains after pelvic anastomoses. One prospective, randomized trial of 100 patients to receive either no drains or closed-suction drains demonstrated that the presence or absence of a drain did not influence the rate of morbidity and mortality. Although there is no evidence for the use of drains when an anastomosis has been made outside the pelvis, pelvic drainage may be important after anterior resection. We recommend placing a drain in extremely low resections, especially where the anastomosis was hand-sewn or in patients who undergo an APR. For all other resections, placement of a drain may be determined on a case-by-case basis.

**CLOSURE**

We prefer to close the abdominal fascia with a looped zero or number 1 PDS suture starting at the cephalad and caudad ends and to run the suture toward the middle. The skin is closed with either staples and a dry sterile dressing consisting of 4 × 8 gauze and Tegaderms (3M, USA) or a 4-0 Vicryl subcuticular suture followed by Dermabond (Ethicon, USA).

**Postoperative Care**

The orogastric tube is removed at the end of the procedure. Intravenous fluids are stopped 6 hours after surgery and the patient can drink sips of clear liquids. The diet is advanced to low residue on postoperative day 1. Heparin is administered subcutaneously at a dose of 5000 units TID. Sequential compression devices are worn by the patient unless the patient is ambulating well. Most patients ambulate on postoperative day 1. The Foley catheter is kept in place for 2 to 3 days. If an epidural has been used for postoperative
pain control, it is usually left in place until the patient is started on oral pain medication.

**Coloanal Anastomosis**

Anastomoses at or just above the anorectal ring often result in increased frequency of stool, incontinence or soilage, and impaired quality of life owing to an insufficient reservoir. Diet restrictions, fiber supplementation, and time after surgery usually will improve these symptoms. Two techniques of reconstruction that also help improve these symptoms in the first year are a side-to-end reconstruction or a colon J-pouch reconstruction when compared to a straight end-to-end anastomosis. In the past, a transverse coloplasty was entertained, but this technique has a higher complication rate and no significant improvement in symptoms so it is of historical interest only.

To create a colon J-pouch, a 6-cm limb of sigmoid or descending colon is folded on itself and the apex is brought down to reach the rectal stump without tension. The splenic flexure may require additional mobilization. Once the apex has been identified a colotomy is made at the apex with Bovie electrocautery, and an 80 GIA linear cutting stapler is used to create the colon J-pouch by stapling out the wall between the two loops of bowel turned on itself, thereby creating a common lumen. A second fire of the stapler may be necessary. This pouch now serves as the neorectum. A double-stapled anastomosis as described above or a hand-sewn anastomosis is then performed. A diverting loop ileostomy is used routinely for these ultralow anastomoses.

Multiple prospective, randomized studies have demonstrated superior function of a coloanal J-pouch over a straight coloanal anastomosis, especially in the first 6 months after ileostomy takedown.

**ABDOMINOPERINEAL RESECTION**

Traditionally, distal rectal cancers have been treated with an abdominoperineal resection (APR), as first described by Miles, who noted high failure rates after local excision. This procedure involves the en bloc resection of the tumor as well as the surrounding lymph nodes and the anal sphincters, resulting in a permanent colostomy.
The APR, although quite successful for early rectal cancers (stage I) in terms of survival, is associated with significant morbidity of 61% and mortality ranging from 0% to 6.3%.\textsuperscript{54} Urinary complications can be as high as 50% and perineal wound infections 16%. In addition to these perioperative problems, significant long-term morbidity is associated with a permanent colostomy. In a patient survey, 66% of patients complained of significant leaks from their stoma appliance, 67% experienced sexual dysfunction, and only 40% of patients working preoperatively ultimately returned to work.\textsuperscript{55} There is also a significant change in body image when compared with sphincter-saving procedures. The 5-year survival rates following an APR range from 78% to 100% for stage I, 45% to 73% for stage II, and 22% to 66% for stage III disease.\textsuperscript{56} Despite radical resection, 20% recur locally. Variations in recurrence rates depend on location of the tumor within the rectum, changes in surgical technique, and the addition of adjuvant therapy. For patients with cancers that involve the sphincter apparatus or for those who are incontinent of feces, an APR is performed to remove the rectal specimen.

**Technique**

The patient is marked preoperatively by the enterostomal nurse for a permanent colostomy. Please see the section Low Anterior Resection with Total Mesorectal Excision for details regarding additional preoperative care, positioning, incision, and rectal mobilization. The dissection proceeds down to the striated muscles of the levator ani; one can confirm muscle contraction by using electrocautery. Once this level is reached, the colostomy is created and the abdominal cavity is closed. The patient is then rolled into the prone position with the buttocks taped apart. The perineal dissection is then performed.

**Perineal Dissection**

The anus is closed with a no. 0 silk suture in a purse-string fashion (Fig. 54-20B). A marking pen is used to draw an ellipse 2 cm outside the superficial external sphincter and extending from the perineal body anteriorly, coccyx posteriorly, and ischial tuberosities laterally. The incision is made with a no.
10 blade and carried down through the dermis into ischiorectal fat (Fig. 54-20C). Two Gelpi retractors are placed at 45 degrees to the anus to facilitate deep dissection. The dissection is carried deep outside the external sphincter toward the tip of the coccyx, keeping in mind the planes of dissection (Figs 54-20A and E). The anococcygeal ligament is palpated just anterior to the tip of the coccyx and it is divided and the retrorectal space is entered. The digit of the surgeon is hooked around the levator complex and this is divided as well. The anterior plane is divided last, taking the specimen off the back wall of the vagina or the prostate. If the two-team technique is used, the perineal incision used is the same as for the prone position. Once the anococcygeal ligament has been divided the palpating finger meets the fingers of a team member working from the abdominal field (Fig. 54-20D). A pair of large scissors is used to poke through the ligament; the scissors are fully spread and, while wide open, are pulled straight back. Hooking the index and middle fingers under the levator muscles and transecting with electrocautery frees the rectum laterally (Figs 54-20F and G).
**FIGURE 54-20** Perineal dissection: two-team synchronous approach. A. Projected lines of pelvic floor resection in the vertical plane. B. Anal closure. C. Perineal incision. D. Incision line anterior to coccyx through anococcygeal ligament through which scissors are used to gain entrance to the pelvis. E. Planes of pelvic dissection and posterior plane of entry into pelvis through the pelvic floor. F. Projected lines of pelvic floor transection. G. Lateral transection of levator ani muscle. H. Anterior transection of rectourethralis, puborectalis, and pubococcygeus. I. Completion of anterior dissection and removal of rectum through perineal wound. J. Pelvic floor closed with two drains in place.

The anterior surface is dissected last (Figs 54-20H and I). The rectum is delivered through the perineal opening. An assistant retracts the skin and subcutaneous tissue anteriorly with an Army-Navy retractor. Care is taken to keep the posterior wall of the vagina or the prostate anterior to the plane of dissection. The surgeon cups the hand around the rectum with traction posteriorly and inferiorly and uses cautery between the rectum and the anterior structures, often reassessing the plane of transection. Once freed circumferentially, the specimen is passed off the field.

The pelvic floor is irrigated and checked carefully for hemostasis. A tongue of omentum or omental pedicle flap may be used to cover the pelvis to prevent the small bowel from dropping deep into the pelvis if radiation is contemplated. Omentum also helps healing, especially in an irradiated perineum or when patients also have undergone prostate or vaginal resections. One or two 19 Fr fluted Blake drains are placed in the pelvis and are brought anteriorly out through the abdominal wall and secured to the skin using 3-0 nylon suture (Fig. 54-20J). The abdomen is closed as described under Low Anterior Resection. The colostomy is matured using interrupted 3-0 Vicryl suture.

If using a two-team approach, the perineal wound can be closed after the pelvis has been irrigated and hemostasis achieved. The remnants of the levators are closed with 0 Vicryl figure-of-eight sutures and then the subcutaneous tissues are closed in two layers of interrupted 0 Vicryl. One layer of 3-0 Vicryl in a deep dermal layer is placed and then the skin is closed with a running 3-0 Monocryl and Dermabond. Because this area is often radiated, multiple layers decrease the risk of the wound breakdown extending into the pelvis.
Initially, the APR was performed utilizing an anterior approach and then flipping the patient for the perineal component. In this way, APR was done by completing the abdominal mobilization of the rectum to the levators circumferentially and then creating a colostomy and closing the abdomen and flipping the patient to complete the perineal portion of the operation. In most institutions two teams work simultaneously (as described previously) and two instrument tables are used with separate counts and often requiring additional OR support staff to assist. All of this increases utilization to save operative time. More recently, attention has reverted to the traditional anterior and posterior approach to the APR. In fact, there are recent data that support a better oncologic outcome using an anterior and posterior approach as described previously. This is known as the cylindrical technique. West et al. reported more tissue excised in all pathologic resections and better margins from the muscularis to all resection margins. These results translated into a lower rate of positive circumferential resection margin with APE 14.8% versus 40.6% for traditional APR and a decrease in intraoperative perforations 22.8% to 3.7%, respectively.\textsuperscript{57} In our experience, we have also found better short-term outcomes with lower perineal wound infections and improved perineal healing.

**Postoperative Care**

Postoperative care is like that described under Low Anterior Resection. The patient can sit starting postoperative day 1 for 30 minutes 3 to 4 times daily for meals if there is no muscle flap reconstruction (in which case sitting directly on the flap is usually postponed for about 4 weeks). Over the next several weeks, the patient gradually increases the sitting time, always utilizing a soft pillow; we do not advocate using a “donut” because the perineum is not supported so it sinks into the donut hole, and this puts tension on the perineal closure. The Foley catheter remains in place for 2 to 3 days.

**Complications**

Perineal wound complications are common following APR and occur in up to 25% of patients. While most of these wound complications are minor, some may require operative debridement. We demonstrated previously that
preoperative radiation and primary closure were not associated with an increased incidence of wound complications compared with nonirradiated patients following APR for rectal cancer.  

Stoma complications include ischemia, retraction, hernia, stenosis, and prolapse. The construction of a good colostomy will provide a patient with a superb quality of life after APR. Early education in the immediate postoperative period allows the patient to adjust to life with a stoma. The stoma shrinks to its final size approximately 6 to 8 weeks postoperatively when the edema has subsided. An end colostomy may be irrigated to establish regularity of bowel movements and further improve the patient’s quality of life. The operative mortality for APRs is less than 2%.

EN BLOC EXCISION WITH RECTUM

Posterior Vaginectomy

Partial vaginectomy is indicated for locally advanced low rectal cancers involving the vagina. One study demonstrated a 5-year survival of 46% and a median survival of 44 months, with most favorable results from negative surgical margins and node-negative disease.

If the patient undergoes an APR, the posterior wall of the vagina is removed as the anterior margin of the resection (Fig. 54-21). After completing the posterior and lateral dissections, the rectum is delivered through the perineum. The anterior aspect of the perineal incision includes the posterior introitus and is extended around the posterior third to half of the vagina only to avoid denervation of the urethra. To achieve hemostasis during the procedure, one can place interrupted 2-0 absorbable full-thickness sutures through the vagina from either side, starting at the apex of the incision, and tie the sutures as the specimen is being excised.
FIGURE 54-21 Posterior vaginectomy with APR. A. Line of dissection, including posterior wall of vagina for low anterior rectal cancer. B. Lines of transection, including posterior wall of vagina.

If the patient undergoes an LAR with a coloanal anastomosis, the partial vaginectomy may be performed through the abdominal approach. The involved area of the vagina is resected with a 1-cm margin and kept en bloc with the rectum. Subsequent closure of the vagina is completed by initially placing Allis clamps on the vaginal edges and then taking full-thickness bites with 2-0 Vicryl sutures in a figure-of-eight fashion.

Before abdominal closure, we recommend placing an omental flap around the vaginal cuff to prevent breakdown of the vaginal suture line. If a coloanal anastomosis is in place, we would position the omentum between the vaginal and the coloanal suture lines.

Prostatectomy

In locally advanced rectal cancer in which there appears to be possible involvement of the prostate, urethra, bladder, or ureterovesicular junction on
CT scan of the abdomen and pelvis, an MRI of the pelvis should be obtained. Urology consult should be made because one must be prepared for radical prostatectomy and/or cystectomy with ileal conduit diversion. A prostatectomy en bloc with rectal resection is an alternative to total pelvic exenteration in patients whose rectal cancer is fixed only to the prostate. The reasons for involving urology are in part due to the vascularity of the prostate. In addition, one should be concerned about constructing any genitourinary anastomosis (eg, between bladder and urethra) in the presence of previous radiation and a rectal anastomosis. Attention should be paid to potential for autonomic nerve deficit if proximity and effacement of the neurovascular bundle are evident on MRI.

**Pelvic Exenteration**

Total pelvic exenteration is an alternative for patients with locally advanced rectal cancer in which the tumor is contiguous with adjacent organs, such as the prostate or bladder (Fig. 54-22). Long-term survival rates range from 20% to 70% and are improved in younger patients with no lymph node metastases.  

Local recurrence rates range from 3% to 8%. An argument against performing total pelvic exenteration is the considerable morbidity (20%-40%) and 0% to 20% mortality associated with this procedure. The most common complications are infection, small bowel obstruction, and problems with urinary diversion.
Prophylactic Bilateral Oophorectomy

Carcinoma of the rectum metastasizes readily to the ovaries. Prophylactic oophorectomy is not routinely advocated for pre- or postmenopausal patients, as prophylactic bilateral oophorectomy does not significantly affect survival. We discuss the potential need for prophylactic oophorectomy if a lesion or nodule is found on the ovary. In postmenopausal women oophorectomy
suffices, and in premenopausal women a biopsy, and if it is positive for invasive cancer then an oophorectomy is performed.

**PALLIATIVE RESECTION IN STAGE IV DISEASE**

Palliative resection of the primary colorectal tumor in stage IV rectal cancer depends on the degree of symptoms present. In patients who are symptomatic from bleeding, localized perforation, and obstruction, there are several management options that can relieve the symptoms of the primary tumor:

1. Permanent diversion followed by chemotherapy (± radiotherapy depending on local symptoms)
2. Palliative resection with a permanent colostomy followed by chemotherapy (radiotherapy is generally not needed if the primary is successfully resected with negative margins in the stage IV patient)
3. Palliative resection with restoration of GI continuity followed by chemotherapy (± radiation depending on the burden of metastatic disease, the resection margins, and any symptoms the patient may develop later from recurrent disease)

In the symptomatic patient, it is our practice to offer upfront surgical resection/diversion and additional therapy using one of the above three options. The surgical procedure depends on the performance status and the intraoperative findings at the time of exploration. In patients with distant spread to solid organs alone, it is our inclination to perform resection of the primary with restoration of GI continuity. In patients with significant peritoneal and pelvic carcinomatosis, we will offer either resection with end colostomy or just a diversion, depending on the degree of pelvic peritoneal carcinomatosis. In the patient with a large burden of disease, it is better to just divert the patient and start chemotherapy and then offer palliative radiotherapy if the bulky primary continues to bleed or causes pain from infiltration of the sacral nerve roots.

On the other hand, resection in the asymptomatic patient with incurable stage IV disease is controversial. Resections for rectal cancer often have significant morbidity and measurable mortality but at the same time offer the
best palliation of local symptoms. Moreover, in the last decade chemotherapy regimens have significantly extended the life expectancy of patients with colorectal cancer. The advent and widespread use of the FOLFOX (5-fluorouracil [5-FU], leucovorin, and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) chemotherapy regimens have extended the median life expectancy of patients with stage IV disease from approximately 8 months to nearly 2 years. Many patients live much longer than this. Hence it is our opinion that upfront palliative resection is warranted in the medically fit patient with a low burden of distant but traditionally incurable disease. In those who have significant distant disease, we prefer systemic therapy with restaging after several courses of chemotherapy. In the medically fit patient with a good performance status that has substantial improvement in the metastatic burden, we will once again offer palliative resection. The choice of operation (see above choices) depends on the intraoperative findings. This approach has never been studied prospectively, and the sparse literature is based solely on retrospective reviews. Despite this, patients who have had asymptomatic primary tumors resected have a substantial survival advantage over those who were never resected. Ruo et al. showed that those who were resected versus the non-resected had a prolonged median survival of 16 versus 9 months and a 2-year survival of 25% versus 6% with both measures reaching statistical significance. Venderbosch et al. in 2011 reviewed all patients enrolled in the CAIRO and CAIRO2 trials who had stage IV incurable metastatic colorectal cancer and they compared patients who had an upfront resection of the primary versus those who did not. In both instances, they found a survival advantage of approximately 6 months for those who were in the resection group.

**LAPAROSCOPIC SURGERY**

Minimally invasive laparoscopically assisted surgery was first considered in 1990 for patients undergoing colectomy for cancer. The technical feasibility of performing laparoscopic TME was demonstrated in several prospective studies. Preservation of the autonomic nerves is also possible during laparoscopic TME. Early results confirmed complete resection of the mesorectum with intact visceral fascia in all patients. Because Nelson others showed equivalent outcome, quality of life, and survival in
laparoscopic surgery for colon cancer, there has been renewed interest in laparoscopic LAR for rectal cancer. The Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (CLASSIC) trial group from the United Kingdom published the results of their randomized comparison of laparoscopic versus open LAR for rectal cancer in 794 patients (526 lap vs 268 open) with a median follow-up of 36.8 months and equivalent numbers of patients receiving chemoradiotherapy. The OS (open 66.7% vs lap 74.6%) and DFS (open 70.4% vs lap 70.9%) were similar in both groups and were without statistical significance. The overall local recurrence rates were 7% in open resection and 7.8% in the laparoscopic group. Even though there was a trend (not statistically significant) toward the laparoscopic group having a higher positive CRM, there was no difference in local recurrence at 3-year follow-up. Long-term follow-up of the CLASSIC trial was published in 2010 and this showed no statistically significant difference in distant recurrence, local recurrence, DFS, or OS. Initially, the increased positive CRM was concerning with only 3-year follow-up. However, with longer-term follow-up the initial increase in positive CRM did not translate into worse outcomes with higher rates of locoregional recurrence. The CLASSIC trial did report overall worse sexual function in men (not women) undergoing laparoscopic rectal cancer resection. Hence patients need to be made aware of the potential for worse sexual dysfunction with laparoscopic surgery for rectal cancer. Finally, the CLASSIC trial measured quality-of-life outcomes for patients undergoing laparoscopic versus open surgery and there were no significant differences between laparoscopic resection and open surgery.

In 2015, the COLOR II trial was published in The New England Journal of Medicine, and the results showed that laparoscopic surgery when compared to open surgery for rectal cancer had similar rates of locoregional recurrence as well as disease-free and overall survival. Three-year results showed that the locoregional recurrence rate was 5% in both groups and that the DFS was 74.8% and 70.8% in the laparoscopic versus open groups, respectively. The OS was 86.7% versus 83.6% in the laparoscopic versus open group again. None of these comparisons was statistically significant. Furthermore, in 2015 both Stevenson and Fleshman published trials in JAMA looking at the efficacy of laparoscopic rectal cancer surgery versus open surgery to establish the noninferiority of laparoscopic resection by examining pathologic specimens. Neither trial yet demonstrates noninferiority because there is no
long-term data for local recurrence, disease free survival and overall survival rates; both authors suggest that laparoscopy should not be considered equivalent to open surgery until long-term clinical outcomes have been established. This has stirred controversy since noninferiority was not proven and all metrics examined were within the established confidence intervals.\textsuperscript{70,71} In summary, nearly all the evidence supports equivalent outcomes with respect to locoregional recurrence, DFS and OS when comparing laparoscopic to open surgery for rectal cancer. There is equivalent quality of life and the potential for worse sexual function with laparoscopy in men. Pending adverse reports of worse clinical outcomes in the long-term follow-up on the two JAMA noninferiority trials (Fleshman and Stevenson), laparoscopic surgery for rectal cancer should be considered equivalent with the above-mentioned caveats regarding sexual function.

**ROBOTIC SURGERY**

In recent years, robotic rectal cancer surgery has begun to take hold. The ROLLAR clinical trial published in 2017 showed that robotic surgery had equivalent results and clinical outcomes when compared to laparoscopic surgery. The primary endpoint of the study was to show that robotic surgery had a lower conversion rate to an open procedure but this was not shown. The conversion rate to open surgery and the rate of positive CRM were equivalent between robotic surgery and laparoscopic surgery. Moreover, there was no difference in the secondary endpoints of urinary dysfunction, sexual dysfunction, intra/postoperative complications, 30-day mortality, and length of stay. Hence it is safe to conclude that robotic surgery offers no advantage when compared to laparoscopic surgery for rectal cancer.\textsuperscript{72} Since laparoscopic and robotic surgery have equivalent results in outcomes, the choice between types of minimally invasive rectal cancer surgery depends on the institution, the surgeon, and patient preference. The main obstacles to robotic rectal cancer surgery (and even laparoscopic when compared to open technique) are the learning curve, time constraints, and the cost of the procedure. Operative time is longer and cost is more substantial in both minimally invasive approaches.

**OTHER TREATMENT OPTIONS**
Besides surgical resection for rectal cancer, there are other options for patients who may not be candidates for surgery owing to their comorbidities, extent of disease, or preference. Endocavitary radiation may be delivered at doses of 50 cGy for palliation and for curative intent. Performed as an outpatient and well tolerated by patients, endocavitary radiation is delivered with sedation and local perineal block.

Electrocoagulation may be used via a transanal approach after administering general anesthesia and placing the patient in the lithotomy position. The rectal lesion and a 1-cm margin are fulgurated. Recurrence rates approach 50% to 80%; therefore, patients may require repeat treatments.

Cryotherapy, another alternative modality, results in a large amount of foul-smelling discharge. Photodynamic therapy has limited availability. Laser vaporization using neodymium: yttrium-aluminum-garnet laser provides palliation but is associated with a 14% recurrence rate and is costly.

**COMPLICATIONS**

Complications of surgical management of rectal cancer may include those common to any major intra-abdominal operation, such as infection, bleeding, wound problems, deep venous thrombosis/pulmonary embolism, myocardial infarction, pneumonia, and renal failure. There are, however, several complications specifically related to rectal cancer. There is a 50% incidence of impotence in men following resection for rectal cancer. Therefore, it is critical to discuss this situation with the patient before the resection and to record the preoperative status of his sexual function. If a man is impotent after surgery, it is advisable to wait 1 year before undergoing implantation of a penile prosthetic device. This delay is recommended not only to ensure that the malignancy has been cleared but also to allow the patient sufficient time to overcome psychological impediments such as a change in body image from pelvic surgery or from a colostomy. Women may also suffer from impaired sexual function, especially if the vagina is distorted during the rectal resection.

A possible permanent colostomy is often not preferred by patients. Its placement, however, must be explained in a way that the patient understands that he or she may be left with this if reconstruction is not technically possible.
Anastomotic leak, which occurs in up to 20% of patients, can be avoided by constructing the anastomosis with well-vascularized tissue without tension. Interestingly, young, muscular men have a higher incidence of anastomotic leaks, which may result from the technical challenge of operating in a narrow pelvis or from strong sphincters that may stress the anastomosis. The latter may be addressed by dilating the anal sphincter in the operating room at the end of the procedure. Anastomotic leaks usually present between 4 and 7 days postoperatively. Symptoms may include fever, tachycardia, arrhythmias, tachypnea, enterocutaneous fistula, or diffuse peritonitis. When a leak is suspected, the patient should be made NPO and blood should be sent for a complete blood count, electrolytes, and type and cross-match. An upright chest x-ray will diagnose pneumoperitoneum. Abdominal series may demonstrate extraluminal air. CT scan of the abdomen and pelvis with water-soluble contrast material may demonstrate abscess formation, extraluminal air, and the actual leak. Barium should be avoided because leakage of barium creates a destructive peritonitis. A leak may be managed with intravenous antibiotics and bowel rest in a patient without peritonitis. An abscess may be drained percutaneously. An enterocutaneous fistula may be treated with total parenteral nutrition and local wound care. If a large leak is demonstrated or the patient experiences peritonitis, exploratory laparotomy with diverting ileostomy or colostomy should be performed. The anastomosis is rarely taken down and should not be reconstructed in the presence of sepsis.

Massive venous bleeding from the presacral space may result intraoperatively from lateral dissection onto the pelvic sidewall or sacrum. Ligation of the iliac vessels is discouraged and may be hazardous. If massive bleeding is encountered, a surgical titanium “tack” may be driven into the sacrum to compress the venous space. Additionally, the pelvis may be packed for 24 to 48 hours, at which time the patient is returned to the operating room for pack removal and closure.

Urinary dysfunction may occur after rectal resection. Many men have coexisting prostatic hypertrophy. Because low rectal dissection approaches the membranous urethra, Foley catheters usually are kept in place for 2 to 3 days. Patients may be discharged with indwelling catheters, especially if they have undergone partial prostatectomies or seminal vesiculectomies. Women may experience urinary incontinence if the anterior aspect of the vagina, which contains the neurologic control of the urethra, is transected.
OBSTRUCTING, METASTATIC, AND RECURRENT RECTAL CANCER

Obstructing Cancer of the Rectum

For obstructing cancers of the rectum, a loop ileostomy, performed as an open or a laparoscopic procedure, is constructed for diversion. Staging of the tumor with ERUS or ecMRI usually reveals locally advanced disease and the patient is then treated with neoadjuvant chemoradiation and considered for subsequent surgical resection.

Metastatic Rectal Cancer

The management of hepatic and pulmonary metastases is not described in this chapter. Nonetheless, if a patient presents with incurable metastatic disease and life expectancy is greater than 6 months, it is reasonable to consider a palliative rectal resection. If the rectal lesion is staged as T3 or N1, we recommend neoadjuvant chemoradiation because this addresses both the primary lesion and the metastasis and may provide some palliation of obstruction, bleeding, or pain. Other options include rectal stents or laser destruction of the tumor to maintain an adequate lumen. It is important to understand the patient, his or her desires, and general state of health when recommending treatment at this stage of cancer.

Recurrent Rectal Cancer

Historically, local recurrence of rectal adenocarcinoma can be seen in up to 30% of patients depending on whether the patient had neoadjuvant or adjuvant chemoradiotherapy in addition to adequate surgery with TME by an experienced surgeon. A good TME in combination with neoadjuvant chemoradiotherapy should yield a local recurrence in the 9% to 13% range. Although recurrence may be seen at the distal margin of the anastomosis, most develop from residual cancer on the pelvic sidewall or inadequate TME with mesorectal nodes that are not excised as part of the endopelvic envelope. The time course for recurrences to present through the anastomosis is
approximately 18 months. By their nature, these tumors are fixed to the pelvic wall and surrounding viscera. They cause significant symptoms, such as intractable pelvic pain, bleeding, cramping or constipation, urinary tract dysfunction, and chronic pelvic sepsis.

When patients present with these symptoms or with a rising CEA level, a workup including CT scan of the abdomen and pelvis, ERUS, MRI of the pelvis, and PET scan may be helpful. A careful pelvic examination is mandatory. A biopsy, either via sigmoidoscopy or CT-guided, should be used to confirm the diagnosis pathologically. If external radiation has not been used before, it should be considered. The surgeon should review the imaging studies and determine which organs are involved, such as the vagina, uterus, prostate, bladder, sacrum, and small intestine, which will require en bloc resection. Urology consult should be obtained if there is any question of prostate or bladder involvement; ureteral stents should be placed preoperatively. Removal of the rectum and urinary bladder with surrounding lymphatic tissue results in a permanent colostomy and ileal conduit.

**INTRAOPERATIVE RADIATION THERAPY**

Intraoperative radiation therapy (IORT) may be considered in patients with pelvic sidewall recurrence. This is performed in an operating room–radiation therapy suite. Resection with negative microscopic margins and absence of vascular invasion independently predicts improved local control and survival after resection and IORT. The major morbidities of IORT include peripheral neuropathy and ureteral stenosis.

**PALLIATION**

These tumors are difficult to palliate, let alone cure. Surgical resection combined with aggressive multimodality therapy is advocated to avert the morbidity of pelvic disease and to prolong survival in a subset of patients, with survival rates up to 30%. Most patients, however, will not be offered curative surgery depending on their comorbidities, poor performance status, distant metastases, or locally unresectable disease on preoperative imaging. These patients may be offered palliative intervention. Miner and colleagues demonstrated that in patients who underwent surgery with palliative intent, improvement was noted in 40% with bleeding, 70% with obstruction, and
20% with pain. When considering the effective use of surgery for these patients, decision-making is complex because one must balance palliation of symptoms, comorbidities, and patient desires and goals. Seeking the input of a multidisciplinary treatment group, including medical oncologists and radiation oncologists, is invaluable.

**CHEMORADIATION**

Patients with rectal cancer who undergo surgery with intention to cure and without evidence of gross disease postoperatively may still develop local recurrence or distant metastases. Up to 10% of patients who undergo TME with tumor-free radial and distal margins may develop local failure. The goal of adjuvant therapy is to eliminate the micrometastatic disease present at the time of surgery.

**Adjuvant Chemoradiation**

In 1990, the National Institutes of Health consensus statement concluded that “combined postoperative chemotherapy and radiotherapy improves local control and survival in stages II and III patients and is recommended.” Most of the information regarding chemotherapy for colorectal cancer comes from trials of colon cancer rather than for rectal cancer. The NSABP C-04 (National Surgical Adjuvant Breast and Bowel Project C-04) trial studied stages II and III colon cancer patients and demonstrated that 5-fluorouracil (5-FU) and leucovorin treatment had a significantly better 5-year survival rate (74% vs 69%) compared with 5-FU and levamisole.

Several trials have suggested a benefit for adjuvant chemoradiation for rectal cancer in patients with resected stage II or III cancers. The GITSG (Gastrointestinal Tumor Study Group) trial demonstrated that combined chemoradiation resulted in an improvement in overall survival as well as a decrease in local recurrence. The NCCTG (North Central Cancer Treatment Group) trial demonstrated that the addition of chemotherapy to radiation reduced both local recurrence (13% vs 25%) and distant metastases (28% vs 46%) and improved survival.

Radiation therapy used alone as adjuvant therapy may improve local recurrence but not survival rates. A theoretical reason to use postoperative
Radiation therapy is that more appropriate patient selection can be achieved because pathologic staging is performed prior to radiation. Disadvantages include radiating the neorectum and small bowel and a lower tendency of patients to complete their radiation. While none of the trials in the 1980s and 1990s demonstrated increased survival, one study did show a decrease in local recurrence.

**Neoadjuvant Chemoradiation**

There are several potential advantages for using neoadjuvant chemoradiation. One is the ability to deliver higher doses of chemotherapy with radiation. Another advantage is tumor downstaging, which has been noted in up to 80% of patients. Moreover, a pathologic complete response occurs in 15% to 30% of patients. The ability to “shrink” the tumor facilitates surgical resection, thereby allowing one to achieve negative margins and perform a sphincter-preserving operation in patients who otherwise would require an APR. Additional advantages include radiating tissues with a greater oxygen supply and then resecting this area and reconstructing and creating the neorectum with nonirradiated colon. Another benefit of neoadjuvant chemoradiation is that the small intestine has not fallen into the pelvis as it will in the postoperative patient; hence there is a decreased likelihood of developing radiation enteritis. Also, patients are more likely to complete the course of radiation therapy because it precedes their surgical resection. Finally, for complete responders it is not uncommon for the oncologist to consider a shorter duration and a less toxic chemotherapy regimen (5-FU/LV vs FOLFOX).

The Dutch Colorectal Cancer Group demonstrated a significantly decreased rate of local recurrence at 2 years in patients who received preoperative radiotherapy (20 Gy over 5 days) followed by TME compared with TME alone (2.4% vs 8%). The Swedish trial was the first and only study to demonstrate a survival benefit (58%) for stage III rectal cancer patients receiving preoperative radiation (short course of 5 Gy over 5 days) followed by surgery compared with patients who underwent surgery alone (48%). The Swedish trial also demonstrated a decreased rate of local recurrence in the radiation-treated group (11%) compared with 27% in the surgery-alone group. Furthermore, a meta-analysis published in *JAMA* in 2000 concluded that preoperative radiation therapy plus surgery compared
with surgery alone significantly reduced the 5-year overall mortality rate, cancer-related mortality rate, and local recurrence rate.\textsuperscript{80}

In the German Rectal Cancer Trial published in \textit{The New England Journal of Medicine}, Sauer et al. randomly assigned patients with clinical stage II or III rectal cancer to preoperative (421 patients) or postoperative (402 patients) chemoradiotherapy based on a concurrent long course of radiotherapy (5040 cGy delivered in fractions of 180 cGy per day, 5 days per week) and 5-FU (120-hour continuous intravenous infusion during the first and fifth weeks).\textsuperscript{81} Six weeks later, TME was performed, followed by four cycles of 5-FU 1 month postoperatively. In this study the median follow-up was 46 months. There was no difference in 5-year overall survival with preoperative versus postoperative chemoradiation (76\% vs 74\%), which was not statistically significant ($p = .80$). Moreover, the patients who received preoperative chemoradiotherapy had a 6\% local recurrence rate as compared to a 13\% local recurrence rate in those receiving postoperative chemoradiotherapy ($p = .006$). Likewise, of the 194 patients who were determined preoperatively by the surgeon to need an APR, 39\% of this group treated with preoperative chemoradiotherapy could have sphincter preservation compared with only 19\% of those patients in the postoperative treatment group ($p = .004$). The neoadjuvant treatment group had less short- and long-term treatment-related toxicity. These differences in local recurrence, sphincter preservation, and treatment toxicities were all statistically significant.\textsuperscript{81} An intention-to-treat analysis of long-term median follow-up of 11 years (134 months) of this cohort of patients revealed that overall survival at 10 years was 59.6\% in the preoperative treatment group and 59.9\% in the postoperative treatment group ($p = .85$). Likewise, the local recurrence rate was 7.1\% versus 10.1\% in the two treatment arms, respectively ($p = .048$) Finally, there were no differences in the incidence of distant metastases or disease-free survival.\textsuperscript{82}

A Polish rectal cancer trial from 2004 compared preoperative short-course radiotherapy (5 days of 5 Gy) versus conventional radiotherapy (28 fractions of 1.8 Gy for a total of 50.4 Gy) to ascertain whether there was a difference in sphincter preservation. The surgical resection was based on the tumor status at the time of surgery not before the radiotherapy. This allowed for the surgical decision to be made after tumor shrinkage for patients who received the longer course of radiotherapy. Between 1999 and 2002 the study enrolled 316 patients. Tumor shrinkage was on average 1.9 cm greater in the long-course group and this was statistically significant. However, sphincter
preservation in the short-course group was 61% and in the long-course group 58%. In other words, whether the patient received short- or long-course radiotherapy, it did not impact sphincter preservation. There was also no difference in survival, local control, or late complications. Furthermore, this Polish trial reported no differences in anorectal or sexual function between the short- or long-course radiotherapy.

A French group in conjunction with the EORTC (European Organization for Research and Treatment of Cancer) group studied “the addition of chemotherapy to preoperative radiotherapy and the use of postoperative chemotherapy in the treatment of rectal cancer.” Patients with clinical stage T3 or T4 rectal adenocarcinoma were randomized to four groups: preoperative radiotherapy, preoperative chemoradiotherapy, preoperative radiotherapy with postoperative chemotherapy, and preoperative chemoradiotherapy with postoperative chemotherapy. This study enrolled 1011 patients; the primary end-point was overall survival and the secondary end-point was local recurrence. The results showed that there was no difference in overall survival between the groups that received chemotherapy preoperatively or those that received it postoperatively. There was, however, a difference in local recurrence. In the patients who received preop, postop, or preop and postop chemotherapy, the local recurrence rates were 8.7%, 9.6%, and 7.6%, respectively, whereas the radiotherapy-alone group had a local recurrence rate of 17.1%. This was statistically significant and it suggests that there is a benefit to local control by adding preoperative chemotherapy to the regimen. It is not clear whether the addition of postoperative chemotherapy to a patient who has already received preoperative chemotherapy with the radiation treatment has any survival benefit.

Our current practice is to recommend preoperative staging with ERUS or MRI to all patients with rectal adenocarcinoma and then to offer chemoradiation to medically fit patients with curative intent who have T3-T4 or node-positive rectal carcinoma. Some patients with bulky T2 lesions near the sphincters should also be considered for neoadjuvant chemoradiotherapy to improve sphincter preservation (Table 54-8). Neoadjuvant therapy then is followed by TME with APR or TME with an end-to-side or colonic J-pouch reconstruction. Postoperatively, patients who have had involved lymph nodes either by preoperative staging or on the final pathology report are encouraged to have additional postoperative chemotherapy. Postoperative chemotherapy
in node-negative patients or patients who have had a complete response is determined on a case-by-case basis.

### TABLE 54-8: CURRENT RECOMMENDATIONS FOR CHEMORADIATION IN RECTAL CANCER PATIENTS AFTER RADICAL RESECTION

<table>
<thead>
<tr>
<th>Stage</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No adjuvant therapy</td>
</tr>
<tr>
<td>II or III</td>
<td>Neoadjuvant chemoradiation</td>
</tr>
<tr>
<td>Low/mid lesion</td>
<td>5-FU-based chemotherapy or other investigational agents with XRT (180 cGy 5 d/wk x 30 treatments) Rest for 4–8 wk Total mesorectal excision Rest for 4 wk Chemotherapy in appropriate patients for 4–6 mo</td>
</tr>
<tr>
<td>High lesion</td>
<td>Pre- or post-op chemoradiation therapy Total mesorectal excision</td>
</tr>
<tr>
<td>IV</td>
<td>LAR or APR for palliation/prevention of obstruction or bleeding Adjuvant chemotherapy 5-FU + leucovorin ± irinotecan or oxaliplatin with individualized XRT</td>
</tr>
</tbody>
</table>

Abbreviations: APR, abdominoperineal resection; 5-FU, 5-fluorouracil; LAR, low anterior resection; XRT, radiation therapy.

There are several in-progress trials that address new and evolving trends in rectal cancer therapy. The Alliance cooperative cancer trial group has the PROSPECT trial, which compares standard therapy of preoperative neoadjuvant chemoradiotherapy for locally advanced rectal cancer to an experimental arm of FOLFOX preop and postop with the elimination of radiation. The primary endpoint is local recurrence, with secondary endpoints being disease-free and overall survival.

A wait-and-watch approach has been advocated for several years by Habr-Gama and colleagues from Sao Paolo. In 2004, they reported on a cohort of patients who were observed after chemoradiation. They initially looked at 265 patients with distal rectal adenocarcinoma who received standard chemoradiation. After 8 weeks, all patients were examined with radiologic and endoscopic means and biopsies. Patients who had negative biopsies and no appreciable ulcer were defined as complete responders and then entered a surveillance program and were designated the observation group (n = 71). This was 26.8% of the original cohort of 265 patients. Patients who had positive biopsies or a large remaining ulcer were considered incomplete responders and were referred for surgery (n = 194). After resection, 22 patients who had a resection were pathologic complete responders. This group was designated the resection group (mean follow-up 48 months) and was compared to the observation group (mean follow-up 57.3 months). Five-
year overall and disease-free survival rates were 88% and 83% in the resection group and 100% and 92% in the observation group.\textsuperscript{86}

Finally, protocols incorporating total neoadjuvant chemoradiotherapy and chemotherapy (total neoadjuvant therapy [TNT]) have been developed and are being utilized in the treatment of locally advanced rectal cancer. The rationale for this approach is twofold. First, the use of neoadjuvant chemoradiation and TME surgery have markedly reduced local recurrence and increased sphincter preservation but distant metastases remain a problem. The benefit of postoperative chemotherapy is not as well documented and understood. In fact, most of the data are extrapolated from colon cancer survival data for adjuvant chemotherapy. Moreover, compliance is not as good as chemotherapy in the adjuvant setting that is not as well tolerated. Hence TNT is being evaluated in phase II and III trials for compliance and efficacy. The goal is to increase completion rates of therapy with decreased toxicity and hopefully decrease distant recurrences.\textsuperscript{87}

**SURVEILLANCE**

After curative resection, long-term follow-up includes routine screening for rectal recurrence and metachronous colorectal neoplasms. Between 60% and 84% of recurrences are seen in the first 24 months and 90% within 48 months. Median time to recurrence is 11 to 22 months. Local recurrence rates range between 4% and 50%. Survival rates vary per stage (see Table 54-4). Median survival after recurrences are detected is 40 months.

Patients are seen postoperatively at 2 weeks and then every 3 months for 2 years. At each visit, the patient undergoes DRE and sigmoidoscopy, and a CEA level is obtained. As per the National Comprehensive Cancer Network (NCCN) guidelines, we recommend at 1 year post-resection a colonoscopy and CT scans of the chest, abdomen, and pelvis. A CT scan is performed annually until 3 to 5 years postoperatively. Colonoscopy frequency is determined by the findings at 1 year. If there are no polyps and no recurrence, the follow-up interval colonoscopy can be lengthened to 3 years, and then if normal even up to a 5-year interval after that. Certainly, in patients who have polyps, Lynch syndrome, or are younger at the initial age of diagnosis, a shorter interval such as every 3 years is recommended. After the initial 2 years of surveillance, patients continue to be followed every 6 months with
CEA levels and physical examinations until 5 years after the surgery. At 5 years, if the patient has had no recurrence, he or she may be followed yearly with clinic visits and may undergo colonoscopy every 3 to 5 years as outlined above. Of course, closer observation is indicated for patients at high risk for subsequent cancer formation, such as patients with IBD, polyposis syndromes, or a strong family history of colorectal cancer.

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59. Ruo L, Paty PB, Minsky BD, et al. Results after rectal cancer resection with in-continuity partial


INTRODUCTION

Cancers of the anus are rare problems with diverse histology. While squamous cell carcinoma (SCC) of the anal canal remains by far the most common of these neoplasms and the main focus of the chapter, the anus may also harbor tumors such as adenocarcinoma, melanoma, and basal cell carcinoma. The treatment of anal cancer has undergone dramatic changes in the last 25 years. Multimodality treatment consisting of radiation and chemotherapy has replaced abdominoperineal resection or wide local excision as the mainstay of therapy. Five-year survival rates now exceed 80% and radical surgery is reserved for cancers of the anal canal that do not respond to chemoradiation or that recur locally. Our understanding of the etiology and epidemiology of anal SCC and its precursor lesions has also profoundly changed in the past few decades yielding new initiatives in both therapy and prevention that may further alter the future treatment of this disease. Anal cancer is clearly a disease that benefits from multispecialty intervention. Because of this, the treatment of anal cancer serves as a paradigm for the multimodality treatment of cancer.
Until recently, discrepancies in anatomic definitions and tumor locations in the anorectal region have made comparisons of therapeutic outcomes difficult. In addition, the evolution of anal canal cancer treatment has resulted in management differences between anal canal and margin tumors that make precise anatomic localization important. In 2000, the World Health Organization refined their definitions of “anal canal” and “anal margin” in the context of histology, the American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) staging system, and traditional anatomic landmarks. This standardized definition is currently used and endorsed by surgeons, pathologists, and radiologists.1

The anal canal extends from the top of the anorectal ring (a palpable convergence of the internal sphincter, deep external sphincter, and puborectalis muscle) to the anal verge (the junction of the anal canal and the hair-bearing keratinized skin of the perineum). The lining of the anal canal is comprised of transitional epithelium as well as non–hair-bearing squamous epithelium. Tumors distal or beyond the verge are termed anal margin or perianal tumors (Fig. 55-1).
FIGURE 55-1  Anatomy of the anal canal and margin.

The anal canal is divided by the anal transition zone (ATZ) into three histologically distinct areas. The ATZ is a circumferential band that extends above and below the dentate line in fingerlike projections that vary in length. Fenger defined the relationship of the ATZ to the dentate line by staining surgically excised specimens with alcian blue—a dye that renders mucin-rich columnar epithelium dark blue, mucin-poor transitional epithelium light blue, and squamous mucosa colorless. He found that the dentate line ranges from 5 to 19 mm above the distal end of the anal canal. The width of the ATZ is generally 1 to 2 cm, projecting 3 to 6 mm below the dentate line. Columnar cells line the anal canal above the ATZ, and squamous epithelium resides below. The ATZ is an area of mixed histology where cuboidal cell types are prevalent. Tumors arising in the anal canal above and within the ATZ are typically nonkeratinizing SCCs. Those originating below this level are generally keratinizing.

Because of the complex gross and histologic anatomy of this region, classification of anal neoplasms has been confusing and inconsistent. According to the World Health Organization classification, anal canal lesions consist of squamous cell (cloacogenic) variants, including keratinizing, nonkeratinizing, and “basaloid” tumors. Other anal canal neoplasms include adenocarcinoma, carcinoid, lymphoma, and melanoma. Anal margin tumors include SCC, giant condyloma (verrucous carcinoma), and basal cell carcinoma.

The dentate line provides an anatomic reference point for lymphatic drainage of the anal canal and margin. Above the dentate line, drainage is primarily via the superior rectal lymphatics to the inferior mesenteric nodes and laterally along the middle and inferior rectal vessels to the internal iliac nodal basin. Lesions distal to the line drain to the inguinal and femoral lymphatics. Tumors in the ATZ may follow both lymphatic routes. Patients with unexplained inguinal lymphadenopathy should undergo a careful examination of the anal canal.

ANAL SQUAMOUS CELL CARCINOMA
Incidence and Epidemiology

The rate of anal cancer has increased from 19/100,000 person-years in 1995 to 78.2/100,000 person-years in 2003. Although this number represents only 1% to 2% of all hindgut cancers, the rise in incidence underscores a significant and serious change in the epidemiology of the problem. Squamous cell cancers of the anus have a viral etiology similar to that of cervical cancer. In the year 2000, approximately 3400 new cases were reported in the United States, but this figure rose to 8080 in 2015, reflecting a trend that mirrors increases in human papilloma virus (HPV) infection.

Until the past decade, the highest rates of anal SCC were described in women, with numbers increasing after 30 years of age to plateau at an incidence of 5.0/100,000 after age 85. The ratio of females to males affected was approximately two to one. However, in the past 10 years, men under the age of 45 who have sex with men (MSM) have constituted the group with the greatest number of reported cases as well as the greatest increase in disease incidence.

Considered as a group, men who practice anal receptive intercourse have an incidence of anal SCC of 35/100,000—a rate identical to that of cervical cancer prior to routine cervical cytological screening. Although not listed as an acquired immune deficiency syndrome (AIDS)-defining illness like cervical cancer, the argument has been made that anal SCC should have similar emphasis. The United States AIDS-Cancer registry is a survey that linked AIDS-related cancer registries in 11 states or metropolitan areas for the period of time between 1995 and 1998 and included over 309,000 HIV-infected patients. The relative risk of SCC-type anogenital cancers in this population was much higher than that of the general population. The relative risks for cervical, vulvar/vaginal, and penile cancers were 5.4, 5.8, and 3.7, respectively, while the risk for anal cancer in women was 6.8 and for men 37.9. Subset analysis of affected individuals revealed that those less than 30 years of age had dramatically elevated relative risks of anal cancer of 134 for women and 162.7 for men. Analyzing the data by HIV exposure history showed that homosexual contact resulted in the highest relative risk of anal SCC, with other categories such as intravenous drug abuse, heterosexual contact among women, and blood transfusion somewhat less.
Etiology, Pathogenesis, and Risk Factors

HUMAN PAPILLOMAVIRUS

Striking evidence, both circumstantial and direct, links HPV infection with the development of both anal SCC and cervical cancer, and it is accepted that these cancers have not only the same etiology and natural history, but a common mode of transmission. Both anal SCC and cervical SCC arise in mucoepithelial histological transformation zones; both are associated with the same oncogenic HPV strains and both have noninvasive precursor lesions. Sexual contact is the mode of transmission of HPV. Women with multiple sexual partners, other venereal diseases, or human immunodeficiency virus (HIV) have a significantly increased risk of developing cervical cancer. Women with a prior history of cervical cancer have a relative risk of developing anal SCC of 4.6.

HPV is a double-stranded DNA virus with a predilection for mucoepithelial tissues. More than 100 HPV strains have been identified, but only approximately 30 have been isolated in cancers of the anogenital region. HPV infection results in either anogenital warts (condyloma accuminata) or squamous intraepithelial lesions (SILs). Condyloma are generally associated with HPV 6 and 11 and their subtypes, and consist of fleshy growths that harbor and generate infectious viruses and have virtually no malignant potential. SILs are graded on the degree to which they exhibit cytologic atypia. In the United States, the Bethesda criteria for anal intraepithelial lesions (AINs) list two dominant categories—high-grade squamous epithelial lesions (HSILs) and low-grade squamous epithelial lesions (LSILs). In the European literature, HSIL is known as AIN 3, whereas LSIL consists of AIN 1 and 2.

The most commonly isolated oncogenic HPV viruses are HPV 16 and 18, which are strongly associated with invasive cancer and are commonly found in both anal and cervical cancer. In a case-control study of 388 patients with anal cancer from Denmark and Sweden, 88% of anal cancers harbored HPV DNA. HPV 16 was detected in 84% of these specimens, whereas no HPV DNA was found in the rectal cancer controls. These investigations have been repeated in SIL with similar results. Studies such as these provide good evidence to support a viral etiology for SIL and anal SCC.
Further characterization of specific viral/cytologic changes have focused on defining the differences between LSIL (AIN 1,2) and HSIL (AIN 3). LSILs can be associated with both low- and high-risk HPV types, although there is a predominance of high-risk types.\textsuperscript{13} It is likely that HSIL contains exclusively high-risk viruses.\textsuperscript{13} It may be possible to base pharmacologic prevention and intervention in SIL and cancer on the genetic differences between these viruses. Therapies may exploit the fact that on the cellular level, LSILs and condyloma support and tightly regulate the viral infectious cycle, resulting in completion of viral replication and production of intact virus.\textsuperscript{13} In contrast, in HSIL, certain genes essential to viral expression are lost, thereby facilitating integration into the host genome and producing incomplete viral replication and genetic instability leading to tumorigenesis.\textsuperscript{13} It is unclear whether persistent viral infection produces increasing cellular atypia that supports this dysregulation, or whether there is something intrinsic and permissive about the anal epithelium itself that allows oncogenic viruses to exploit the cell cycle.

**HUMAN IMMUNODEFICIENCY VIRUS INFECTION**

There is an increased incidence of both anal SCC as well as its precursor lesion HSIL in patients with HIV infection. Data collected in case control studies among homosexual men and heterosexual women with high-risk behaviors show a direct correlation between HIV seropositivity, HPV prevalence, and anal cancer and its precursors. Epidemiologic evidence among homosexual men in the San Francisco Bay area documents a dramatic rise in anal SCC between 1973 and 1999 when the relative risk increased from 3.7 to 20.6.\textsuperscript{15} Similar studies conducted in New York City between the years 1979 to 1985 show a tenfold increase in anal SCC in men 20 to 49 years of age coinciding with the explosion of HIV in this population at this time.\textsuperscript{11} However, HPV, HSIL, and anal cancer are not phenomena linked exclusively to homosexuality. Similar findings occur in HIV-infected male heterosexual IV drug users who deny anal receptive sex. In this cohort, a high rate of HPV infection coincides with an elevated rate of HSIL as well as anal cancer.\textsuperscript{16} Heterosexual women who are HIV positive or have progressed to AIDS have high rates of HSIL as well.\textsuperscript{8} When HIV-positive and -negative cohorts (both male and female) with similar HPV risk factors are compared, the rates of both HSIL and anal cancer are dramatically increased in the HIV-
positive groups.\textsuperscript{8–11}

Although the resultant decline in cell-mediated immunity in HIV-infected patients seems to correlate with HPV infection, the exact mechanism of potentiation is unknown. In fact, there is evidence to support the hypothesis that HPV may represent an opportunistic infection assisted by retroviral preinfection.\textsuperscript{8} It is uncertain whether the level of immunity and the severity of HIV infection as measured by CD4 counts directly correlate with HSIL or SCC rates in cervical or anal cancer. However, several studies done in the past 10 years have demonstrated an inverse relationship between CD4 counts and progression from LSIL to HSIL, supporting a causal relationship between cell-mediated immunosuppression and high-risk phenotypes.\textsuperscript{12} Conversely, a recent subgroup analysis of a 202 member HIV+ cohort receiving highly active antiretroviral therapy (HAART) for 6 months indicates that the rates of HPV infection, HPV levels, and progression of anal dysplasia remained unchanged in spite of significant improvement in CD4 counts.\textsuperscript{4,8} Longer follow-up is needed to determine whether advances in the treatment of HIV will correlate with lower rates of HPV positivity, anal dysplasia, and anal cancer.

Persistence of high-risk HPV types 16 and 18 in HIV infected individuals is a well-documented problem. Lingering infection, immunosuppression, and the presence of the HIV virus may all be factors contributing to a lack of viral cell-cycle regulation, increased proliferation, diminished apoptosis, and faulty DNA repair. These individuals have a twofold increase risk over non-HIV infected patients of progression from LSIL to HSIL within 2 years of diagnosis, and have a relative risk of anal cancer of 63.4 over the general population.\textsuperscript{13}

**SMOKING**

Cigarette smoking is a well-known risk factor for anal SCC that is independent of sexual practices. The risk increases two- fivefold over that of the general population.\textsuperscript{11,17} It is speculated based on data demonstrating an increased incidence in premenopausal women of 5.6 with a 6.7% linear increase per pack-year that smoking may have an antiestrogenic effect permissive for the disease in the estrogen-sensitive tissues of the anal canal.\textsuperscript{18} This hypothesis is supported by the finding that no risk increase was
demonstrated by this study in either male or postmenopausal female smokers.

**CHRONIC INFLAMMATION**

At one time, benign anorectal conditions such as hemorrhoids, fissures, and fistulas were thought to predispose to the development of SCC. The etiology or common mechanism was presumed to be prolonged exposure of the anal canal epithelium and margin to chronic inflammatory conditions. Patients with inflammatory bowel disease (IBD) were believed to be at increased risk, particularly when anal fistulas were present. In 1994, Frisch examined this issue in a large population and found no evidence to support a causal relationship between benign anorectal conditions and anal cancer up to 13 years after resolution of the benign condition. In another large population study, Frisch identified 9602 Danish patients with a diagnosis of either Crohn’s disease or ulcerative colitis with a mean follow-up time of 10 years. Only two patients developed anal SCC during this time. Both patients had the disease longer than 15 years. Although long-term IBD patients may be at slightly increased risk of anal SCC, short- and mid-term risk is not significantly different from that of the general population.

**Anal Intraepithelial Neoplasia**

No discussion of anal SCC would be complete without a consideration of its precursor lesion, AIN. The term HSIL is synonymous with AIN 3 (European designation), “carcinoma-in situ,” and “Bowen’s disease.” Bowen’s disease is still a term often used to describe this entity and may refer to scaly, pruritic low-profile inflammatory perianal manifestations of AIN. Until recently, wide local excision had been the treatment of choice for HSIL (Bowen’s disease). It was assumed, based on anecdotal evidence, that a percentage of patients with HSIL progress to invasive cancer. This led to attempts to surgically clear patients of the disease. Recent advances in the understanding of the natural history of LSIL, HSIL, and anal cancer have more clearly defined the risk of dysplasia, leading many to adopt a policy of either very specific “high-risk” ablative therapy or close and frequent observation.

The incidence of anal cancer among HIV-positive homosexual men is 75 to 80/100,000 (a rate of .8/100,000 in the general population), more than
twice the incidence of cervical cancer in women (35/100,000) prior to the introduction of routine cervical Pap smear cytology evaluations.\textsuperscript{8,16} Because of the dramatic reduction in cervical cancer (8/100,000 currently) attributed to the detection of dysplasia, it is widely believed that the same result could be seen in high-risk anal cancer populations if similar detection and ablation methods are used. A predicate to this hypothesis, however, is to better establish the role of equivalent potential precursor lesions in the development of invasive anal cancer.

There is a very high incidence of HSIL in the same population affected by high rates of anal cancer. In a study of 67 HIV-positive homosexual men (MSM) and 50 HIV-positive IV drug users who denied anal intercourse, HSIL was present in 85% of the MSM group and 46% of the IV drug users.\textsuperscript{21} In a large group of HIV-positive women followed by the Women’s Interagency HIV Study, 6% of HIV-positive and 2% of HIV-negative women had HSIL.\textsuperscript{22} Seventy-nine percent of HIV positive women in this study were HPV positive.\textsuperscript{23} A similar result was documented in the University of California San Francisco (UCSF) Anal Neoplasia Registry, where the vast majority of HIV-positive (93%) and -negative (61%) homosexual men had HPV infection whereas only 5% of the HIV-positive and only one HIV-negative man had HSIL.\textsuperscript{23} Cytologic testing (anal Pap smears) in this group was abnormal in 60% of the HIV-positive and 21% of the HIV-negative men.\textsuperscript{24} Clearly, abnormal anal cytology does not necessarily correlate with HSIL. Furthermore, it is clear that not all patients with HSIL progress to invasive cancer. Not enough longitudinal studies have been conducted, however, to specifically quantify the risk associated with either the presence of HPV or HSIL. The 4-year projected incidence of HSIL in HIV-positive men in the study mentioned is 49% and in HIV negative homosexual men it is 17%.\textsuperscript{24} Ongoing studies will help establish actual rates of conversion to invasion, associated risk factors, and high-risk populations.

**DIAGNOSIS AND TREATMENT OF HSIL**

A growing awareness of the natural history of anal cancer has resulted in an increase in diagnosis of the problem in high-risk populations. Anal cytology (similar to cervical Pap smears) is currently being used by some as a screening tool for the detection of anal dysplasia in high-risk populations. Prior to the present understanding of the pathogenesis of anal cancer, HSIL
was most commonly (25%-40% of cases) discovered as an incidental finding after hemorrhoidectomy. Other patients came to attention with scaly, raised, lesions at the anal margin. Because the majority of patients diagnosed are asymptomatic, the true incidence of HSIL is not known presently. Future studies following patients with abnormal anal cytology may clarify this number.

Anal screening (Pap smears) was first described in the 1990s as a direct corollary of cervical Pap smears and has since been promoted as a diagnostic and screening tool in high-risk populations. However, evidence demonstrating a resulting decrease in incidence of anal cancer similar to that of cervical cancer has not been forthcoming. The use of anal cytology as a screening technique has not gained the recognition afforded cervical Pap smears. Lack of recognition by clinicians of the increased incidence of anal cancer, limitation of the problem to high-risk populations, lack of knowledge of techniques, cost, and a dearth of supporting outcomes data may all conspire to limit the perceived usefulness of the tool. Ongoing outcome studies may clarify the role of anal Pap smear for high-risk patients.

A 1999 survey of the practice patterns of members of the American Society of Colon and Rectal Surgeons revealed that 86% to 95% surgeons treated HSIL with wide local excision. A distinction was made between “microscopic” disease and other manifestations. Most HSIL found incidentally in hemorrhoidectomy specimens were considered microscopic asymptomatic disease were and simply followed without re-excision (74%). This survey coincided with other investigations highlighting the multifocal nature of HSIL and the difficulty presented by wide local excision under these circumstances. In one review, of 34 patients undergoing wide local excision for macroscopically evident HSIL, 19 had positive margins at the time of initial resection, and 12 of the 19 had recurrent HSIL within one year. Even with a microscopically complete initial resection, 2 of 15 patients eventually developed HSIL. Although none of these individuals subsequently developed anal cancer, five developed significant surgical complications of resection including anal stenosis and incontinence.

A growing recognition of the morbidity of surgery for HSIL, particularly asymptomatic microscopic disease, in light of the uncertain natural history of anal neoplasia and dysplasia, has resulted in uncertainty concerning appropriate treatment. In the early 1990s, high-resolution anoscopy (HRA)
was developed at the UCSF. Like anal Pap cytology, HRA is a direct application of the technology for cervical intraepithelial detection and ablation to anal dysplasia. The technique can be done in either the office or, for anal margin involvement or more extensive disease, in the operating room. After obtaining a Pap smear, a digital rectal exam is performed followed by placement of a cotton swab covered in gauze soaked in 3% acetic acid. The swab is held in place for 1 minute, after which an anoscope is inserted permitting examination of the anal canal by a colposcope providing 6× to 25× magnification. Special attention is directed to the area surrounding the ATZ. Applying acetic acid causes these often unapparent lesions to become opaque or “acetowhite.” Lugol’s iodine solution is then placed in the anal canal to further highlight these areas. HSILs fail to take up Lugol’s, rendering the area yellow to tan, whereas normal tissue or LSILs stain dark brown or black. This approach, combined with the magnification, allows visualization of vascular changes such as punctation, mosaicism, and atypical vessels characteristic of dysplastic change. Suspicious lesions are then destroyed by electrocautery or laser. Over 400 patients have been prospectively evaluated at UCSF with HRA. Patients with findings of HSIL have gone on to HRA with ablation. Over 75% of HIV-positive patients with “extensive” circumferential disease have had recurrent HSIL on follow-up (2.5 years). None of these patients have thus far developed anal cancer.

There are no prospective studies or published reports documenting the rate of progression of HSIL to invasive cancer. While treatment strategies for anal HSIL vary widely, no approach has been conclusively shown to reduce anal cancer incidence. The rate of HSIL progression to anal cancer has, based on clinical models, been proposed as 1% per year. Because the rate is so low and the natural history of HSIL as yet unknown, chemotherapy and radiation is unwarranted. Wide local excisional techniques that compromise form and function may also be too drastic given the apparent low malignant potential of HSIL. HRA with ablation may specifically eradicate early invasive lesions and aggressive precursors, but data supporting that position does not yet exist. Furthermore, HRA ablative therapy does not eliminate the need for follow-up.

While many clinicians advocate a program of close follow-up consisting of digital rectal exams and unmagnified anoscopy at regular intervals, this approach, too, is unvalidated. HRA may provide objective evidence of the presence of disease that office examination alone does not. Whether ablative
therapies should follow documentation of HSIL by any method remains unknown and controversial. ANCHOR (ANal Cancer/HSIL Outcomes Research) is a randomized clinical trial that started accruing in 2015 and is designed to definitively address the question of utility of anal pap smears and HRA by randomizing more than 5000 HIV-positive persons with HSIL to either treatment or close monitoring without treatment. The outcome of this study will hopefully answer this question.83

HUMAN PAPPILOMAVIRUS VACCINES

Administration of the HPV vaccine is considered primary prevention in the treatment of cervical cancer and is very effective in prevention of both high-grade lesions and cancer as well as condyloma. A similar strategy is employed in the prevention of anal cancer. In a randomized, blinded trial, 602 sexually active MSM were randomized to receive three doses of the quadrivalent HPV (qHPV against serotypes 6, 11, 16, 18) vaccine or placebo and evaluated every 6 months by HRA and HPV testing over 3 years. Significant reduction of anal HSIL associated with any type of HPV occurred in those who received the qHPV compared with placebo. Another study evaluated 112 HIV-positive men (ages 27 or older with no evidence of anal HSIL) with the three-dose course of qHPV vaccine and found seroconversion in all of these subjects. The quadrivalent HPV vaccine has been demonstrated to be effective and safe in HIV-infected men. When incidence of anal cancer is used as an endpoint, it has been found that qHPV vaccination of HIV-negative MSM treated for anal HSIL reduced the lifetime risk of cancer by 60.77%. When costs of vaccination were balanced against costs of treatment, vaccination compared very favorably. The 9-valent (9v) HPV vaccine became available in 2015 and proved efficacious and safe in a large randomized trial of over 14,000 women. It provided protection against serotypes 6, 11, 16, 18 that was noninferior to that of the quadrivalent vaccine with additional extended coverage. Although no current data exist, it is assumed that the 9v HPV vaccine would provide a similar response to the quadrivalent vaccine in high risk populations.13

Pathology, Diagnosis, and Staging of Anal Squamous Cell Cancer
PATHOLOGY

Nearly 80% of anal canal tumors are either SCCs or histologic variants of SCC (Fig. 55-2). The great variation in terminology results from the histologically diverse microscopic anatomy and the fact that many tumors, especially in the ATZ, have a mixed histologic appearance including squamous, basaloid, and rarely, glandular elements. The World Health Organization designates all squamous carcinoma variants in this location as “cloacogenic.”³ Tumors of the distal anal canal, and particularly of the anal margin, are generally comprised predominately of squamous cells, with fewer basaloid and no glandular characteristics.²⁸ The more distal in the anal canal the squamous tumor arises, generally, the more likely it is to contain keratinizing cells. Tumors of the proximal anal canal and ATZ are usually composed of nonkeratinizing cells.²⁹ It is important to note that the difference in the cellular characteristics of these anal canal cancers does not result in a different mode of treatment. There are no data to suggest differences in outcome between squamous and basaloid histologic types in anal canal cancers. Anal margin tumors, however, are typically treated like skin cancers by local excision.
The treatment of anal canal cancer has undergone major changes within the past 25 years. Currently, chemotherapy and radiation is usually the sole treatment for patients with localized disease. Prior to 1974, standard-of-care was either wide local excision if the tumor was judged to be superficial or abdominoperineal excision for tumors invading the sphincter. Outcomes were poor, with overall survival rates after abdominoperineal resection (APR)
ranging from 30% to 70%, depending on tumor grade, stage, and size.\textsuperscript{29} The local recurrence rate after wide resection or APR was reported to be 25% to 35% with a 100% local recurrence rate for tumors invading through the submucosa in a series from Singh and associates at Roswell Park Memorial Institute.\textsuperscript{30} Perineal or pelvic recurrence occurs in 50% to 70% of patients undergoing APR, with less than 10% dying of distant disseminated disease.\textsuperscript{7} In 1974, Norman Nigro, at Wayne State University, used radiation and fluoropyrimidines in anal canal cancer as a way to reduce local recurrence.\textsuperscript{31} He observed that often there was no residual cancer in the resected specimen. Thus began an exciting and revolutionary time in the treatment of this disease that resulted in a radical shift in treatment.

**DIAGNOSIS AND STAGING**

Over 50% of patients present with a complaint of rectal bleeding. Delays in diagnosis are common because the tumor is often mistaken by both patients and physicians for benign conditions such as hemorrhoids or fissures. Pain, tenesmus, and pruritus may be present. The initial physical examination should include a digital rectal exam, proctoscopy, and palpation of the inguinal lymph nodes. A biopsy of the anal mass is necessary to confirm the diagnosis. Inguinal masses should be aspirated with a fine needle for diagnosis and staging. Because the current nonoperative approach to anal cancer management is highly effective, excisional biopsy of suspected anal squamous cell cancers and inguinal node dissection for adenopathy should be avoided. The staging process is completed by computed tomography of the chest, abdomen, and pelvis and an MRI of the pelvis to assess depth of invasion and aid in establishing the size of the tumor.

The International Union Against Cancer (IUCC) staging system for anal cancer was updated in 2010 and adopted by the AJCC (Table 55-1). In contrast to staging parameters for other gastrointestinal lesions, it is based upon size rather than depth of invasion. Anal margin tumors are staged the same as skin cancers.

| TABLE 55-1: AJCC STAGING SYSTEM FOR ANAL CANAL CARCINOMA |
Primary Tumor (T)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor not assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II-III, high-grade anal intraepithelial neoplasia)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2 cm but ≤5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;5 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder</td>
</tr>
</tbody>
</table>

Regional Lymph Node (N)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis in inguinal, mesorectal, or internal iliac lymph nodes</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis in external iliac lymph nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>Metastasis in external iliac with any N1a nodes</td>
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Distant Metastasis (M)

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<td>No distant metastasis</td>
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<tr>
<td>M1</td>
<td>Distant metastasis</td>
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AJCC PROGNOSTIC STAGE GROUPS

<table>
<thead>
<tr>
<th>When T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the stage group is...</th>
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<tbody>
<tr>
<td>Tis</td>
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<td>M0</td>
<td>0</td>
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</tr>
<tr>
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<td>N1</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
</tr>
<tr>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>IIIB</td>
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<td>N0</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
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<td>N0</td>
<td>M0</td>
<td>IIIIB</td>
</tr>
<tr>
<td>T4</td>
<td>N1</td>
<td>M0</td>
<td>IIIIC</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>

HISTOLOGIC GRADE (G)

<table>
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<tr>
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</thead>
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<td>Grade cannot be determined</td>
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<tr>
<td>G1</td>
<td>Well differentiated (low grade)</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated (low grade)</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated (high grade)</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated (high grade)</td>
</tr>
</tbody>
</table>

¹Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

A number of reviews in the literature prior to and during the introduction of chemoradiotherapy for anal SCC document the strong correlation between tumor size, lymphatic spread, and prognosis. In a 1984 report from MD Anderson Cancer Center, 132 patients treated by abdominoperineal resection for anal SCC were studied. For patients with tumors 1 to 2 cm in size, survival was 78%, 3- to 5-cm tumors had survival of 55%, and patients with tumors >6 cm experienced survival of only 40%. Other reviews suggest that survival for large tumors is considerably worse, at less than 20%, and that generally, overall survival is diminished when tumor size is greater than 5 cm, whether the tumor is treated by excision or chemoradiotherapy.

The presence of regional nodal metastases is a poor prognostic indicator regardless of treatment modality. Although survival in the face of nodal metastases has improved significantly with the use of chemoradiation, patients who present with metastatic disease have a significant survival disadvantage. Prior to the routine use of chemoradiotherapy, a report in which surgery was done with and without preoperative radiation demonstrated a 5-year survival rate of 44% for node-positive patients compared to 74% for node-negative patients. Other studies confirm comparatively poor survival for patients with nodal metastases.

**Surgical Management**

Operative therapy for anal canal SCC has largely been supplanted by chemoradiation and is now the exception rather than the rule. Historically, the failure rate for APR has depended rather predictably on the size of the primary tumor. This procedure was often accompanied by prophylactic inguinal node dissection, but the morbidity and lack of efficacy caused routine inguinal lymphadenectomy to be abandoned. Failure rates for APR range from 40% to 70%, with local failure rates of 40% and median survival time after recurrence of only 1 year.

Although chemotherapy and radiation have been shown to result in higher disease-free survival rates, there may still be a role for local excision in some cases of anal canal carcinoma. A retrospective analysis of local excision at University of Minnesota revealed a direct correlation between survival and tumor size. For tumors greater than 2.5 cm, 5-year survival rates were 60%.
Although the sample size was small, the authors advocated local resection with curative intent only for small (<1 cm) well-differentiated tumors confined to the submucosa, for which survival rates were greater than 90%. Corman and Haggitt reported a similar experience, with all tumors confined to the submucosa being cured by local excision or APR, and those invading more deeply suffering eventual local recurrence. Longo recorded a 62% failure rate in Stage I to III tumors undergoing solely local excision in which all patients with Stage II and III tumors recurred. Tumor accessibility, full-thickness excision, depth of invasion, and negative margins seem imperative technical considerations when considering local resection. Even so, very few candidates are suitable for this approach.

**NEOADJUVANT MULTIMODALITY THERAPY**

National Comprehensive Cancer Center (NCCN) guidelines specify concurrent chemoradiotherapy with 5-FU and mitomycin C (MMC) as the optimum regimen for the treatment of anal SCC. Phase III trials of radiation in doses of 50 to 60 GY with either MMC or cisplatin as single agents have been confirmed to prove the best overall survival, disease-free survival, and colostomy-free survival with the least toxicity when compared to either radiation alone or radiation with combination MMC and cisplatin together. Chemoradiotherapy is highly successful in early stage (T1 and T2) cancers, with complete tumor regression in 80% to 90% of patients. Any therapy or combination of therapies is less successful in T3 and T4 tumors or those with locoregional nodal metastases at diagnosis. Intensity-modulated radiotherapy (IMRT) seems to offer better local control with less toxicity to surrounding organs when compared to 3D conformational radiation.

The treatment of anal canal carcinoma has changed radically since the late 1970s. In 1974, Norman Nigro, a colorectal surgeon at Wayne State University, defined a treatment protocol involving the administration of 5-FU, MMC, and preoperative radiation to shrink anal canal tumors. Fluoropyrimidines were known at the time to enhance the effect of radiation, and there was some evidence that MMC had an antineoplastic effect on squamous cell tumors. Nigro’s protocol was neoadjuvant, and the radiation (30 Gy total) was given in 15 sessions over a 3-week period. The 5-FU was administered at a dose of 1000 mg/m^2/day for 4 days, starting on the first day.
of radiation therapy, as a continuous infusion. It was then repeated on days 29 through 32. MMC (15 mg/m$^2$) was administered as a single dose on treatment day one.\textsuperscript{32} Of the three patients in the initial report, two underwent APR 6 weeks after treatment. The third refused surgery and remained disease free. No evidence of tumor was found in the specimens of the two patients who underwent surgery.\textsuperscript{32}

Following the dramatic results reported by Nigro’s group, others followed suit, treating patients with radiation alone and with multimodality therapy followed by surgical excision. In 1983, Michaelson et al. at Memorial Sloan Kettering Cancer Center (MSKCC) reported that 52\% of patients treated with both chemotherapy and radiation had a complete pathologic response and another 22\% had only microscopic disease at operation.\textsuperscript{40} All of these patients had undergone APR or wide local excision following treatment. After Nigro’s 1974 publication, a number of other investigators examined the effects of multimodality therapy. Most used 5-FU and MMC as the chemotherapeutic regimen, although several made dose and infusion modifications, and nearly all increased the radiation dose. Maximal doses were in the range of 50 Gy. Because of such variability among therapies, meta-analysis is difficult. Even now, variability in dosing, both for chemotherapy and radiation, and variability in outcome metrics make comparing existing phase III data difficult.

Preliminary studies done by Nigro and others set the stage for prospective phase II studies. Because MMC was observed to contribute significant toxicity to the regimen, RTOG 8704 was designed to randomly compare 5-FU+radiation versus 5-FU+MMC+radiation directly.\textsuperscript{41} The oncologic benefits of the MMC were immediately obvious, resulting, in spite of higher toxicity, in significantly higher disease-free survival. Similarly, radiation alone was tested on the theory that chemotherapy-related toxicity could be spared, but the stage-for-stage local control rates dropped to 45\% to 55\% of study subjects. A series of randomized trials in both Europe and the US followed, all confirming that multimodality therapy significantly improved both disease-free survival as well as endpoints such as colostomy free survival. All except the small Action Clinique Coordonnees en Cancerologie Digestive (ACCORD-03) used concurrent 5-FU+MMC. ACCORD-03 used 5-FU+cisplatin.\textsuperscript{42}

The current recommendation of chemotherapy and radiation resulted in
overall survival rates of 78% in the MMC arm of the RTOG 9811 trial, 79% in the MMC arm of the Anal Cancer Trial II (ACT II), and 71% in the cisplatin arm of ACCORD-03.\textsuperscript{42,43,44} Because these studies were designed to compare radiation regimens as well, optimal ranges of radiation were able to be determined. Higher doses of radiation were not found to be beneficial to achieve local control; indeed, doses of 50 to 60 Gy were found to promote fecal incontinence. Also, these studies failed to demonstrate any benefit in the use of cisplatin over MMC in terms of disease-free or progression-free survival (Table 55-2).

<table>
<thead>
<tr>
<th>TABLE 55-2: RANDOMIZED PHASE III TRIALS OF RADIATION AND CHEMOTHERAPY FOR ANAL CANAL CANCER</th>
</tr>
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<tbody>
<tr>
<td>Radiation dose and type have been particularly difficult to analyze because of variability of techniques, doses, and boosts to both the primary site as well as the inguinal lymph nodes. However, some conclusions can be drawn based on existing recent phase III evidence. In general, small, early-stage tumors localized to the anal canal respond well to lower doses of radiation (in the 30-50 Gy range). Larger, more advanced T3 and T4 tumors and those &gt;5 cm are notoriously difficult to control with any technique and generally higher doses have been used to treat. Minimum total doses of 45 Gy for early tumors with increased doses to 54 Gy for larger tumors is a guideline. Higher rates of radiation beyond 54 to 56 Gy seem to result in higher colostomy rates. The colostomy rates associated with multimodality therapy reached 14.5% in the ACCORD-03 study, 5% in the RTOG 9811 trial, and 12.5% in ACT II. Both colostomy and fecal incontinence rates are both probably directly attributable to the late effects of radiation\textsuperscript{45} (Fig. 55-3).</td>
</tr>
</tbody>
</table>
Palpable inguinal lymph nodes should be evaluated by fine needle aspiration at the onset of treatment for staging. Several reviews have confirmed the poor prognostic outlook conferred by inguinal lymph node (LN) metastases. In 1970, Stearns reviewed the MSKCC experience with anal canal cancer and noted that only 14% of patients with synchronous nodal metastases survived for 5 years. Similarly, O’Brien reported in 1982 that none of the 52% of patients presenting with synchronous LN involvement survived more than 3 years after diagnosis. Both Stearns and O’Brien observed independently
that patients presenting with metachronous LN metastases had better survival following therapeutic inguinal LN dissection.\textsuperscript{47} In the MSKCC review, 75% of patients survived longer than 5 years after groin dissection.

The use of radiation to the inguinal lymph nodes, both prophylactically and for treatment was explored by Papillon.\textsuperscript{48} In 1974, he reported on 19 patients with synchronous inguinal nodal involvement who underwent groin irradiation for disease control. Eleven of the 19 had no evidence of disease at 3 years. Cummings group treated nodal disease in a similar fashion and showed that 87% of patients had good disease control or cure without groin dissection.\textsuperscript{49}

With the use of radiation fields expanded to include inguinal, internal, and external iliac nodes, the current treatment paradigm is to treat synchronous inguinal nodal metastases with chemotherapy and radiation along with the primary tumor. Metachronous LN involvement is treated with salvage chemotherapy and radiation if dose limits have not been exceeded as well as groin dissection if warranted.

**Management of HIV-Positive Patients**

Treatment for anal cancer does not differ in the HIV-positive population. Combined chemotherapy and radiation is the best approach to this disease in the setting of HIV/AIDS. Studies have consistently documented responses to standard therapy that equal those in the HIV negative population.\textsuperscript{16} However, experience with treatment in this population is limited, confined mostly to retrospective reviews with historic comparisons. Although the time period of treatment is often only 6 weeks in duration, it can be complicated by moist desquamation, diarrhea, perineal pain and tenderness, and severe anal pain. Late effects include anal stenosis, necrosis, chronic ulcer formation, and compromised continence in both the HIV-positive and -negative populations. Severe toxicity may require diverting stomas in 6% to 12% of HIV-negative patients with an even greater rate in the HIV-positive population.\textsuperscript{8} Symptoms of acute toxicity are generally manageable with good skin care, antidiarrheals, and narcotic analgesics. Even so, there is widespread concern regarding the degree and management of these toxicities in the HIV-positive patient and some evidence to suggest that they are significantly more severe, resulting in treatment delays or dose reductions. At the UCSF, toxicity
requiring hospitalization, dose reduction, or treatment delays occurred in 82% of patients undergoing standard high-dose therapy.\textsuperscript{8} For patients with a baseline CD4 count under 200, the rates of toxicity were especially severe: 50% of these patients required fecal diversion.\textsuperscript{8} A review of patients treated from 1985 to 1998 by Orkin’s group compared treatment toxicity and tolerance of 13 HIV-positive with 60 HIV-negative patients.\textsuperscript{50} Although demographics of the HIV-positive patients were different from that of the comparison group, there was no difference in treatment or stage at diagnosis. Acute toxicity occurred in 80% of the HIV-positive patients versus 30% of those who were HIV negative. Late toxicity (40% vs 16%) and rates of local control (38.5% vs 15%) were also compromised in the HIV-positive cohort.

The impact of HAART on the treatment of anal cancer in the HIV population is not well understood at this time. Several small series have published reports suggesting that HAART improves tolerance to anal cancer therapy. Stadler et al. at the University of Texas Southwestern Medical Center examined the effects of treatment in HIV-positive patients before and after the advent of HAART.\textsuperscript{46} The group found the average CD4 count of the HAART patients was significantly higher, and that this seemed to correlate with better disease-free survival. All six pre-HAART patients died with active disease, with a 2-year survival rate of 17%. Of those on HAART, the 2-year survival rate was 67% with 4/8 patients remaining free of disease.

A preliminary review of 11 HIV-positive patients at UCSF receiving both HAART and chemoradiation with baseline mean CD4 counts above 300 further delineates the difficulties treating this population.\textsuperscript{8} Although ten patients completed therapy, eight of ten developed severe acute toxicity and two had chronic complications requiring colostomy. Three of the eleven died of disease within 13 months of diagnosis, and two have undergone APR for local recurrence.\textsuperscript{8} It is clear that although HAART has extended and improved the lives of those infected with HIV, it has not necessarily provided protection against the toxicities of anal cancer treatment in those patients.\textsuperscript{51} At this time, however, it seems prudent to deliver standard therapy (4500-5400 Gy, MMC, and 5-FU) to those HIV-positive patients in good health, and to monitor closely for side effects. HIV patients with very low CD4 counts (<200) and significant comorbidities may require individualized regimens, closer monitoring, or treatment breaks.
Recurrent Disease and Salvage Therapy

The goal of early detection of local post-treatment recurrence is to prevent lymphatic spread of disease and maximize salvage. Most clinicians advocate a thorough physical exam including a digital rectal exam and anoscopy every 3 to 4 months for at least 2 years. Suspicious lesions are then sampled either in the office or operating room should they arise.

There is some evidence that local regression of disease following radiation therapy can occur up to 6 to 9 months following chemoradiation. Routine biopsy of the anal canal following treatment is no longer recommended within this time period. Rousseau et al. advise allowing the anal canal to heal completely, reserving biopsy for nonhealing ulcers and recurrent or enlarging anal canal masses after a period of at least 6 months following therapy. After this point, any disease detected is “residual,” and salvage therapy is warranted.

In spite of success with nonoperative anal canal cancer management, depending upon the stage of disease, 10% to 30% of patients will recur—most locally. The treatment of recurrent or persistent disease is APR with negative margins. In a retrospective analysis of salvage therapy for recurrent disease following chemotherapy with radiation, Allal and colleagues found that APR results in a 53% actuarial 5-year survival rate versus 28% in those who didn’t receive additional treatment. Pocard’s data from St. Antoine University Hospital examined salvage APR in 21 patients who had either residual disease after sphincter conservation or recurrence. The group found an actuarial 5-year survival benefit of 30%. Factors resulting in failure were lymphadenopathy, positive margins, and distant disease. Longo et al. compared salvage with chemoradiation versus APR and found that only 27% of patients treated with additional combined therapy survived long-term, whereas 57% of those in the APR group did (Table 55-3).
Patients with recurrence die of locoregional complications including ureteral obstruction, perineal sepsis and necrosis, bowel obstruction, and venous thrombosis. Contraindications for salvage surgery include medical debilitation, known distant metastases, invasion of the pelvic sidewalls, and obvious inguinal lymphadenopathy. The preoperative assessment should include a chest CT or positron emission scan and an MRI or CT scan of the abdomen and pelvis with oral and intravenous contrast. A multidisciplinary approach is appropriate for local invasion of resectable structures such as the urinary bladder, cervix, vagina, or the sacrum. A team including a urologist, neurosurgeon, orthopedic surgeon, and plastic surgeon may be required. Recurrences close to the pelvic sidewall may be indistinguishable intraoperatively from fibrosis and scarring from prior radiation or surgery. An intraoperative frozen section may be useful if considering placing after-loading catheters or delivering intraoperative brachytherapy to these areas. The role and long-term outcomes of brachytherapy as a treatment adjunct for salvage surgery have not yet been validated.

The complications of salvage pelvic surgery may be severe and debilitating and include perineal wound dehiscence and necrosis. Tissue coverage in previously irradiated fields improves wound healing, and many consider it essential for post-exenteration reconstruction. Pedicle and rotational flaps may be fashioned from the gluteus, gracilis, or rectus abdominus muscles.

Data documenting long-term follow-up in patients salvaged with radiation or chemoradiation following local excision are lacking. The patients who undergo primary excision for anal canal carcinoma do so for a number of reasons including polypectomy, hemorrhoidectomy, or excisional biopsy as well as local excision with intent-to-cure. Although it is unclear at this point whether further treatment for completely excised, early-stage lesions is appropriate, patients with positive margins, or those with tumors harboring vascular or lymphatic invasion with poorly differentiated characteristics are
candidates for further therapy. A retrospective analysis from MSKCC in 1999 reviewed 14 patients who received postoperative chemoradiation (either 30 or 45-50 Gy) after local excision.\textsuperscript{61} Actuarial 5-year local control rates were 93\% with no differences between outcomes in the higher and lower dose groups. Longo published the largest single retrospective analysis of outcomes in 1994 reviewing chemoradiation following local excision.\textsuperscript{39} The overall local control rate at 5 years was 79\% in 109 patients receiving a median dose of 42 Gy. Stratification of the data by stage revealed 90\% local control rate with Stage I, 54\% Stage II, and 100\% Stage III (6/6 patients).\textsuperscript{39} There have been no prospective studies comparing local excision alone versus chemoradiation for TI favorable-histology tumors. However, current studies suggest that tumors that are incompletely excised, have poor histologic characteristics, or are Stage II and above are candidates for chemoradiation following excision.\textsuperscript{65,68,74} As with primary therapy, giving chemotherapy (principally infusional 5-FU with mitomycin-C or cisplatin) seems to promote effective local control at lower radiation doses.

Anal canal carcinoma metastasizes in 10\% to 20\% of patients late in the course of disease and prognosis is exceedingly poor.\textsuperscript{7} Liver and lung metastases predominate and cisplatin-based chemotherapy is the only strategy shown to be somewhat effective.\textsuperscript{65}

**ANAL MARGIN CANCER**

SCC of the anal margin is at least five times less common than anal canal carcinoma, and for the most part is treated by primary surgical excision similar to skin cancers. These tumors arise on the perianal skin beyond the anal verge (Fig. 55-4). They are usually well or moderately differentiated keratinized SCCs and generally have a favorable prognosis.\textsuperscript{7} Metastases are late and rare, and recurrences are typically locoregional. Symptoms include pain, bleeding, itching, and palpable mass. In a study from Denmark, Jensen noted a 6-month median duration of symptoms prior to diagnosis with an erroneous initial diagnosis made in 29\% of cases.\textsuperscript{62} Because these tumors are fairly slow-growing and uncommon, they are frequently mistaken for hemorrhoids or other benign conditions at initial presentation.
FIGURE 55-4 Anal margin tumor.

Diagnosis is often suspected by the experienced clinician on inspection, but biopsy prior to definitive treatment is imperative. If the lesion is small, excisional biopsy can be accomplished with adequate margins (1 cm). If the tumor is larger, a small incisional biopsy allows accurate classification of the tumor and appropriate preoperative counseling.

Metastases to the inguinal lymph nodes occur in 15% to 25% of patients. The rate of nodal metastases is directly proportional to the size of the tumor. Papillon and Chassard reported that for tumors less than 2 cm in size, the rate of nodal metastasis was 0%; 2 to 5 cm (24%); greater than 5 cm (67%).\(^{63}\) Cummings found that those with tumors less than 5 cm in size had 0% rate of nodal metastases, whereas metastases occurred in 25% of those with tumors 5 cm or larger.\(^{64}\)

**Surgery**

Although surgical excision (either local excision or APR depending upon location) is considered standard-of-care for anal margin tumors, outcomes data for this rare neoplasm are primarily retrospective. In most studies, overall and disease-specific survival are considered for all stages together, and subgroup analysis for large numbers of patients is not available.
Unfortunately, evaluation of local recurrence data is similarly limited by the small numbers of patients affected; however, in general, a trend toward increased recurrence in larger tumors is apparent.\textsuperscript{65} Surgical treatment of the primary anal margin tumor is accomplished by wide local excision with 1 cm margins. At MSKCC, Greenall et al. reported a series of 51 patients with SCC of the anal margin.\textsuperscript{66} Five-year survival was 88\% although local recurrence was 46\%. Local recurrences were amenable to re-excision. Inguinal nodal dissection was employed for metachronous inguinal nodal metastases. Thirteen patients in this series underwent APR as initial treatment. The local recurrence rates for these patients was identical to that of the local excision group. Tumor size was the most important factor for local control and survival (\textsuperscript{\textit{Fig. 55-5}}). In 1979, Cleveland Clinic reviewed their experience with surgery for anal margin tumors over a 20-year period.\textsuperscript{67} Eight patients were identified for whom follow-up was available. A disease-specific survival rate of 70\% was noted after 8 years, with a local recurrence rate of 30\%. At the University of Chicago, a 19\% local recurrence rate was noted in 16 patients undergoing surgical therapy alone.\textsuperscript{68} Two of eleven patients recurred following local excision, and one of three recurred after APR. Of 27 patients with either Stage I anal margin cancer or carcinoma-in-situ treated at Mayo Clinic between 1950 and 1970, 5-year survival rates were 100\%, although local recurrence rates were unavailable.\textsuperscript{69}
After surgery alone (local excision or APR), the overall survival rate for all stages is 60% to 90% with a local recurrence rate of approximately 30%. Survival rates after surgery for recurrence are unknown.\textsuperscript{70}

**Radiotherapy**

The optimal treatment of anal margin tumors is dependent upon location. Significant challenges and functional problems may result when the anal
sphincters are present within the boundaries of optimal surgery. If adequate excision compromises the sphincters, abdominoperineal resection is an option. However, many surgeons and oncologists would advocate a more conservative approach and use radiotherapy. Cummings et al. demonstrated local control rates of 100% for anal margin tumors less than 5 cm in size with a dose of 50 Gy over 4 weeks. Local control rates were inversely proportional to the size of the tumor. For those tumors 5 to 10 cm, 70% local control was achieved, but for tumors greater than 10 cm, only 40% sustained a durable response. Similar results were reported by Papillon and Chassard at Centre Leon Berard in France. In this review, a 78% overall survival rate was achieved using external beam (40 Gy cobalt 60 source) with a perineal field. Again, those with tumors greater than 5 cm in size fared considerably worse, with overall survival rates less than 50%.

There have been numerous retrospective reviews of the response of anal margin tumors to radiation in the past 40 years documenting stage-specific local recurrence rates, disease-specific survival rates, and overall survival rates. Overall, local control rates of 52% to 87% are typical, with 5-year overall survival rates ranging from 52% to 90%. T1 and T2 tumors have better local control rates and overall and disease-specific survival rates ranging from 82% to 100%.

It is difficult to evaluate the sphincter preservation rate from these reviews. Small numbers and retrospective design limits direct comparison of this technique to surgery alone. There are no prospective studies comparing surgery alone to radiotherapy. Although the addition of chemotherapy (5-FU and MMC or cisplatin) seems logical, there are few data to support that approach. The rationale for these agents is extrapolated from the prospective trials of chemoradiation in the setting of anal canal carcinoma. Even so, it is reasonable to believe that primary radiotherapy with or without chemotherapy for anal margin tumors in close proximity to the anal sphincters, where adequate excision may compromise function, will result in both sphincter preservation and good local control. It is also reasonable to expect that surgical salvage for recurrence after primary radiotherapy is a possibility, with rates of local control of approximately 50%. Long-term disease-specific survival following this scenario is unknown.

**ANAL MELANOMA**
Melanoma of the anus and rectum is a rare malignancy accounting for less than 1% of all colorectal and anal neoplasms. After the skin and eye, the anorectum is the third most common site of melanoma. Although there is a female predominance with an almost 1:2 ratio, there is evidence that the median age of affected males is significantly less (57 vs 71 years of age). Cagir et al. examined the epidemiology and demographics of anorectal melanoma using the Surveillance, Epidemiology, and End Results (SEER) database. These investigators note a recent emergence of a bimodal age distribution of anorectal melanoma for all patients, with males occupying the younger aspect of the curve. Survival rates were slightly better in this group (63% vs 51% at 1 year and 41% vs 27% \( p < 0.01 \) at 2 years).

Most common symptoms include bleeding, itching, presence of a mass, pain, tenesmus, or changes in bowel habits. Like anal SCC, misidentification of the tumor as a hemorrhoid is a common mistake. Diagnosis is frequently made following hemorrhoidectomy or local excision of the perianal mass. The tumor can appear small and polypoid, or large and ulcerating. About 30% of these tumors are amelanotic and unpigmented, making immediate recognition of the problem difficult. On pathology, 70% of lesions show some evidence of melanin production either grossly or microscopically. Commonly, anal melanoma arises at the mucocutaneous junction. Occasionally, the lesion arises more proximally, within the rectal mucosa. Although the origin of these tumors is speculative, they are believed to arise in areas of heterotopic anal canal epithelium in the rectum or to start from proximal microscopic mucosal spread from a small lesion located more distally.

### Staging and Prognosis

Like melanoma of the skin, anorectal melanoma is staged by depth or thickness of the lesion. Lymphatic metastases can occur in the inguinal, mesorectal, and internal iliac nodal distribution. Mesorectal LN metastases are found in 40% to 60% of patients at initial presentation and inguinal adenopathy is present in at least 20%. Distant spread occurs to the bone, lung, and liver. Regardless of stage, 5-year survival rates for patients diagnosed with anorectal melanoma are very poor, averaging about 6%. The median survival
time following diagnosis is 12 to 18 months.\textsuperscript{70}

**Surgery**

In recent years, local excision has replaced APR for the treatment of anal melanoma. Outcomes data comparing local recurrence rates and survival do not demonstrate a survival difference between the two approaches; therefore, the preservation of fecal continence is a priority when possible. A number of retrospective series published from 1985 to 1990 reviewing institutional experience with local excision and APR found that 5-year survival rates range from 0\% to 29\% for those undergoing wide local excision and from 0\% to 26\% for those undergoing APR.\textsuperscript{72,73,74}

Even though survival differences are minimal between local and radical approaches, local recurrence rates may be higher after local excision. A study from MD Anderson Cancer Center found that recurrence after local excision was significantly higher than recurrence after APR (58\% vs 29\%), and that median survival times were the same (approximately 19 months for both groups).\textsuperscript{74} Patients in this study with local recurrence developed synchronous regional and distant disease. Roumen’s group in the Netherlands also reported an increased rate of local recurrence with local excision, but no overall survival disadvantage.\textsuperscript{75} Based on these data, wide local excision with negative margins is the treatment of choice for those patients without anal sphincter involvement.\textsuperscript{78}

Inguinal LN dissection in anorectal melanoma is usually reserved for those with clinically positive nodes and is a palliative intervention. Prophylactic nodal dissection does not seem to provide a survival benefit and there currently is no clear indication for it. The role of sentinel LN mapping in this disease is not clear. The benefits of the technique are now well established in cutaneous melanoma, but it has not been investigated in anorectal melanoma and is not currently routinely performed.

**Adjuvant Therapy**

Checkpoint inhibitors are currently used in the treatment of cutaneous melanoma. It confers a survival benefit in this group, improving disease-free survival rates, sometimes dramatically. There are scant data demonstrating its
efficacy in anorectal melanoma, however, and current reports of adjuvant chemotherapy in this setting are not robust. External beam radiation for symptomatic pelvic and local recurrences and metachronousinguinal nodal disease has been incorporated into the palliative treatment of anorectal melanoma, but again, no data are available to assess overall efficacy. It seems reasonable, however, to extrapolate treatment paradigms from cutaneous melanoma to anorectal melanoma in Stage IV disease.

The surgical treatment of anorectal melanoma has changed over time, evolving from radical to local excision. No survival benefit is conferred by APR in most studies, and in most reviews survival is quite poor in spite of surgical excision, with median survival less than 20 months from the time of diagnosis. Although adjuvant chemotherapy and immunotherapy is shown to be effective in cutaneous melanoma, lack of data hinders acceptance of this therapy in anorectal melanoma.

**ANAL ADENOCARCINOMA**

Anal adenocarcinomas are uncommon, comprising 10% of all anal canal carcinomas.\(^7\) Symptoms of bleeding, pain, and change in bowel habits are nonspecific and similar to other anal canal and distal rectal neoplasms. Anal adenocarcinomas may occasionally be found in chronic anal fistulas.

Although outcomes data are few, anal adenocarcinoma has a poor prognosis when compared to rectal cancers or anal SCC. In small series, 5-year survival rates range from 64% to less than 5%.\(^7\) These neoplasms have a high rate of both local and distant failure.\(^7\)

Treatment is similar to therapy for adenocarcinoma of the rectum. Neoadjuvant chemoradiation followed by surgical excision is recommended. Postoperative adjuvant chemotherapy may be prudent, as it is in rectal adenocarcinoma, to reduce the risk of distant spread.

**PAGET DISEASE**

Paget disease was first described in 1874 by Sir James Paget who reported 15 cases involving the nipple.\(^\) Paget’s has a female predominance (1.5:1) with a median presentation age of 65 years.\(^7\) The disease is usually present for an extended period of time prior to diagnosis because the symptoms are
nonspecific and often mistaken for a benign dermatitis. Paget’s occurs in apocrine, hair-bearing areas. Erythematous, pruritic, scaling plaques with well-defined serpiginous borders are a typical feature of the disease. These lesions may also appear ulcerated and crusty with a serous discharge. The disease can be found in both the anal canal and margin.\textsuperscript{78} Histologically, Paget disease is defined by the presence of large intraepidermal anaplastic tumor cells lying separately or in small clusters. Perianal Paget cells are foamy and vacuolar in appearance and stain light blue with hematoxylin and eosin. They are positive for PAS, mucicarmine, alcian blue, and cytokeratin 7.\textsuperscript{78}

The pathogenesis of Paget disease is still somewhat unclear. Because it can be associated with the presence of rectal adenocarcinoma, it is speculated that Paget’s represents a downward extension of the tumor or that a “neoplastic milieu” may create an environment hospitable to the presence of multiple gastrointestinal primary tumors. Another hypothesis holds that it is a primary tumor of the apocrine glandular elements of the distal anal canal and margin. Others have suggested that Paget’s may arise from a neoplastic pluripotent epidermis basal cell.\textsuperscript{78}

Perianal Paget’s is associated with an underlying visceral malignancy in 20% to 86% of cases.\textsuperscript{78} Colorectal adenocarcinoma is the most common synchronous tumor, but urogenital, breast, and bile duct carcinomas have also been reported. Screening for other malignancies is imperative. A colonoscopy and prostate exam are basic preventive and diagnostic tests that can be helpful. Some authors recommend CT of the abdomen and pelvis as well.

Complete excision is the treatment for Paget disease. The extent of the disease is usually determined by taking circumferential biopsies of the anal canal and margin. After the disease is mapped, wide local excision is performed. Often, the procedure creates large defects that may require skin grafts or flaps (rotational, island, or myocutaneous). Because excision to negative margins is critical to cure, techniques to ensure this may be required. Surgeons may obtain frozen sections of the margins of the specimen in the operating room prior to reconstruction. Some surgeons prefer to cover the wound with saline-soaked gauze, admit the patient to the hospital, and await permanent pathology results for up to 2 to 3 days prior to reconstruction. If a large flap reconstruction is placed in the anal canal, some recommend diversion with a colostomy or ileostomy at the time of the perineal excision.
Recurrence rates as high as 61% have been reported following excision of perianal Paget disease.\textsuperscript{79,80} Re-excision is the usual recommendation, although in cases where underlying rectal or anal adenocarcinoma exist, radiation followed by abdominoperineal resection is advisable. Although recurrence rates are high, the prognosis of Paget’s limited to the perianal area with no concomitant neoplasm is very good.\textsuperscript{80} Because of the association with additional visceral neoplasms, continued surveillance is required for patients with perianal Paget disease. Physical examination, including a prostate and pelvic examination, and periodic colonoscopy are probably prudent. Biopsies of new lesions at the edges of the flap or graft may reveal residual disease. Local excision of these recurrences and continued surveillance is required.

**BUSCHKE-LÖWENSTEIN TUMORS**

Buschke-Löwenstein tumors are also referred to as “giant condylomas” and were first described in 1925 by Buschke and Löwenstein as “carcinomalike condyloma acuminata.”\textsuperscript{81} They are rare entities belonging to a wider group of lesions called “verrucous carcinomas,” which includes oral and cutaneous fungating condylomas. The key feature of giant condyloma that differentiates it from benign anal condyloma is the presence of local invasion.

Although the natural history of these lesions is poorly understood, the etiology is assumed to be similar to that of condyloma. HPV has been isolated from the tumors. Histologically, the lesions are benign in appearance and do not invade the basement membrane as carcinomas do. Instead, they destroy surrounding tissue by expansion rather than direct invasion. The tumor does not metastasize. Deaths from untreated Buschke-Löwenstein tumors have occurred following deep invasion into unresectable pelvic structures followed by superinfection and recurrent sepsis. Overall mortality rate from this rare entity is 20%.\textsuperscript{82}

Because there are so few cases reported, there are no consistent treatment guidelines. Primary treatment consists of surgical resection to clear margins.\textsuperscript{82} However, adequate surgery may be impossible when the tumor deeply invades the pelvis. There have been several case reports demonstrating the efficacy of intralesional injection of interferon-α 2b.\textsuperscript{81} At least three reported cases of deeply infiltrating giant condyloma have
completely responded to long-term therapy including one patient who would have required hemipelvectomy with limb amputation to achieve negative margins. Interferon-α 2b may be a good alternative or supplement to radical resection in select cases. Long-term outcomes are not available.

**REFERENCES**


LIVER
HEPATIC ABSCESS AND CYSTIC DISEASE OF THE LIVER

Nikolaos A. Chatzizacharias • Kathleen K. Christians • Henry A. Pitt

INTRODUCTION

The differential diagnosis of cystic lesions of the liver includes bilomas, abscesses, parasitic disease, simple cysts, polycystic liver disease, biliary cystadenoma, and cystadenocarcinoma. The disease spectrum includes infectious, traumatic, congenital, and neoplastic hepatic lesions, which are relatively uncommon. Although significant improvements have been made in the diagnosis, treatment, and outcome of many of these cystic hepatic lesions, controversy continues regarding the best treatment option. Many classification systems exist for these lesions; however, the one used in this chapter is presented in Table 56-1.

TABLE 56-1: CLASSIFICATION OF CYSTIC HEPATIC LESIONS
I. Infectious hepatic cysts
   A. Pyogenic liver abscess
   B. Amebic liver abscess
   C. Hydatid liver cysts
II. Congenital hepatic cysts
   A. Simple cysts
   B. Polycystic liver disease
III. Neoplastic hepatic cysts
   A. Cystadenoma
   B. Cystadenocarcinoma
IV. Traumatic hepatic cysts

PYOGENIC LIVER ABSCESS

The first description of a hepatic abscess is credited to Hippocrates in the year 4000 BC. Ochsner’s classic 1938 paper\textsuperscript{2} described this disease as one that occurred in young males with pylephlebitis, usually due to appendicitis, and resulting in liver abscess. At that time, pyogenic liver abscesses carried a case-fatality rate of 77\%\textsuperscript{,2} and open surgical drainage remained the treatment of choice for many years. In 1953, McFadzean and associates\textsuperscript{3} in Hong Kong advocated closed aspiration and antibiotics for treatment of solitary pyogenic liver abscess; however, this treatment did not gain widespread acceptance until imaging advancements in the 1980s allowed for precise localization and a percutaneous approach to treatment. In recent decades, the predominant etiology of pyogenic liver abscess has changed from pylephlebitis to a biliary origin, and more recent reports from Asia and the United States have noted an increase in incidence of cryptogenic liver abscesses. Fortunately, advanced imaging techniques and improved therapeutic modalities have decreased the case-fatality rate for this disease to 6\% to 26\%.\textsuperscript{4,5}

Etiology

Kupffer cells act as a filter for the clearance of microorganisms in the liver. These organisms reach the liver through the bloodstream, biliary tree, or direct extension. Abscesses occur when normal hepatic clearance
mechanisms fail or the system is overwhelmed. Parenchymal necrosis and hematoma secondary to trauma, obstructive biliary processes, ischemia, and malignancy also promote invasion of microorganisms.

In order to appropriately treat the abscess, source control is required. Six distinct categories have been identified as potential sources: (1) bile ducts, causing ascending cholangitis; (2) portal vein, causing pylephlebitis from appendicitis or diverticulitis; (3) direct extension from a contiguous disease; (4) trauma due to blunt or penetrating injuries; (5) hepatic artery, due to septicemia; and (6) cryptogenic (Fig. 56-1).


Biliary disease accounts for 35% to 40% of all pyogenic liver abscesses, and 40% of pyogenic liver abscesses of biliary origin are related to an underlying malignancy. Obstruction of the biliary tree is the norm, and
cholangitis is present in up to one-half of these patients. Intrahepatic stones and related biliary stricture are predominant in Eastern series, whereas malignant biliary obstruction is more common in the West. Any manipulation of the biliary tree—namely cholangiography, percutaneous transhepatic stents, endoscopic stent placement, and biliary-enteric anastomoses—also predisposes patients to cholangitis and pyogenic liver abscess. Malignancy contributes to poor nutrition and immunosuppression, potentiating the whole process.

Intestinal pathology is responsible for 20% of all pyogenic liver abscesses. Transient bacteremia due to bacterial translocation or frank gastrointestinal perforation causes overwhelming numbers of microorganisms to spread via the portal venous system to the liver. In the preantibiotic era, 43% of Ochsner’s 622 patients seeded the liver through the portal vein, and appendicitis was the most common source (34%). Today, appendicitis accounts for only 2% of all pyogenic liver abscesses. Diverticulitis, perforated colon cancers, and abscesses elsewhere in the abdomen and pelvis remain common causes of pyogenic liver abscesses. Primary and metastatic liver tumors may also become colonized with enteric flora.

Contiguous extension of gangrenous cholecystitis, perforated ulcers, and subphrenic abscesses also is a reported source for pyogenic liver abscess. In addition, liver trauma causes parenchymal necrosis and clot, which creates an ideal milieu for the seeding and proliferation of microorganisms and subsequent abscess formation. Microorganisms can then seed these areas of necrosis through intraoperative contamination, biliary-enteric anastomoses, external drains involving the biliary tree, or percutaneous drains placed near the site of trauma or ablation.

Arterial embolization of bacteria via the hepatic artery causes approximately 12% of pyogenic liver abscesses. Intravenous drug abuse accounts for most of these cases, but hepatic artery chemoembolization or particle embolization as well as umbilical artery catheterization also have been cited. Liver abscess formation has been described as a complication in less than 5% of hepatic transarterial embolizations and less than 1% of tumor ablations. Arterial embolization also can occur from distant infection in the heart, lungs, kidneys, bones, ears, and teeth.

Cryptogenic abscesses occur in 10% to 45% of patients, depending on the aggressiveness of investigation used to define the source. Patients with
cryptogenic abscesses usually have comorbidities such as diabetes, immunosuppression, or malignancy. Abscesses in these patients tend to be solitary and usually contain a single anaerobe.

**Incidence**

Pyogenic liver abscess affected 5 to 13 patients per 100,000 admissions prior to 1970 and accounts for approximately 15 cases per 100,000 admissions today. Seeto and Rocky\textsuperscript{11} reported an incidence nearly two fold that of earlier reports (22 per 100,000). This rising incidence is attributed to a more aggressive management approach to hepatobiliary and pancreatic cancers as well as major improvements in diagnostic imaging.\textsuperscript{7,12}

**Predisposing Factors**

Pyogenic liver abscesses occur more frequently in adults with comorbid conditions including diabetes mellitus, cirrhosis, pancreatitis, inflammatory bowel disease, pyelonephritis, and peptic ulcer disease. Solid organ cancers, as well as lymphoma and leukemia, are present in 17% to 36% of patients with liver abscesses.\textsuperscript{8} Branum and associates\textsuperscript{13} reported an increased incidence in patients with underlying malignancy and immunosuppression. Civardi and colleagues\textsuperscript{14} and Lambiase and coworkers\textsuperscript{15} have reported series of patients with liver abscesses and underlying acquired immune deficiency. The combination of chemotherapy and steroid use is thought to be responsible in these cases.

In addition to comorbidities, age plays a role in the development of pyogenic liver abscess. The age of patients with pyogenic liver abscess has increased since 1938. This disease has now become a disease of the middle-aged and elderly, with a reported mean age of 47 to 65 years. Older patients are more likely to have a biliary etiology or underlying malignancy, whereas younger patients are more likely to be alcoholic males with a cryptogenic origin. Polymicrobial or anaerobic infections with multidrug-resistant organisms, a pleural effusion, inappropriate initial antibiotic selection, and a greater severity of illness on admission occur more frequently in older patients. Underlying malignancy is more prevalent in older patients and is a risk factor for developing anaerobic infections. Age and an Acute Physiology
and Chronic Health Evaluation II (APACHE II) score ≥15 on admission are risk factors for case fatality in older patients. The case-fatality rate in older patients is related to host conditions, rather than characteristics of the abscess itself. Clinicians should apply an aggressive approach for older patients exhibiting a poor response to primary treatment, particularly in those with a greater severity of illness on admission.16

In children, pyogenic liver abscesses tend to occur in the setting of host-defense abnormalities or immune disorders. Complement deficiencies, chronic granulomatous disease, leukemia, and other malignancies place these children at increased risk for liver abscess. Hepatic abscesses also are seen in sickle cell anemia, congenital hepatic fibrosis, polycystic liver disease, and after liver transplantation (Table 56-2).8

<table>
<thead>
<tr>
<th>TABLE 56-2: PREDISPOsing FACTORS FOR PYOGENIC LIVER ABSCESSES</th>
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<tbody>
<tr>
<td><strong>Children</strong></td>
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<tr>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Complement deficiencies</td>
</tr>
<tr>
<td>Leukemia</td>
</tr>
<tr>
<td>Malignancy</td>
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<td>Sickle cell anemia</td>
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<td>Polycystic liver disease</td>
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<td>Congenital hepatic fibrosis</td>
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<td>Posttransplant liver failure</td>
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<tr>
<td>Necrotizing enterocolitis</td>
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<tr>
<td>Chemotherapy and steroid therapy</td>
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<td>Acquired immunodeficiency syndrome</td>
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**Pathology**

The source of the liver abscess is predictive of the number, location, and size of the abscess affecting a given patient. In general, portal, traumatic, and
cryptogenic hepatic abscesses are solitary and large, whereas biliary and arterial abscesses are multiple and small. Huang and associates\textsuperscript{7} reported that 63\% of patients had abscesses involving the right lobe, 14\% had abscesses involving the left lobe, and 22\% had bilobar disease. The number of bilateral and multiple abscesses has increased as more patients present with a biliary etiology. Bilateral disease may be seen in 90\% of patients with an arterial or biliary source. In contrast, those with intra-abdominal infections frequently present with right lobe abscesses due to preferential flow from the superior mesenteric vein. Fungal abscesses are usually multiple, bilateral, and miliary.\textsuperscript{8}

**Bacteriology**

Diagnostic confirmation of a pyogenic liver abscess involves aspiration of the abscess itself and obtaining blood cultures that are positive. Abscess cultures are positive for growth in the majority of cases (80\%-97\%), whereas blood cultures are positive in only 50\% to 60\% of cases.\textsuperscript{11,14} *Escherichia coli*, *Klebsiella* species, enterococci, and *Pseudomonas* species are the most common aerobic organisms cultured, whereas *Bacteroides* species, anaerobic streptococci, and *Fusobacterium* species are the most common anaerobes.\textsuperscript{12} Huang and colleagues\textsuperscript{7} cited the increased use of indwelling biliary stents as the cause of an increasing incidence of *Klebsiella*, streptococcal, staphylococcal, and pseudomonal species in liver abscesses. They also noted the presence of fungi in 22\% of cultures taken between 1973 and 1993 compared to only 1\% between 1952 and 1972. Broad-spectrum antibiotic use in the treatment of cholangitis was thought to be the causative factor. *Candida* fungal abscesses also are found in cancer patients who have undergone cytotoxic chemotherapy. *Mycobacterium tuberculosis* is a common infecting organism in acquired immunodeficiency syndrome\textsuperscript{9} (Table 56-3).

| **TABLE 56-3: ORGANISMS ISOLATED FROM PYOGENIC LIVER ABSCESSES** |
The species of microorganism found in a hepatic abscess is related to the source. The biliary tree gives rise to abscesses predominantly comprised of *E. coli* and *Klebsiella*. *E. coli*, enterococci, and anaerobes are the main organisms recovered from abscesses related to the intestinal tract. Anaerobes are the usual microorganisms found in cryptogenic liver abscesses in Western countries. Negative cultures may relate to poor anaerobic culture technique or the use of broad-spectrum antibiotics prior to abscess drainage. In series where careful attention is paid to anaerobic organism recovery, anaerobes may be detected in 10% to 17%, most often *Bacteroides fragilis*. If suspected bacterial cultures are repeatedly negative, amebic and parasitic
organisms must be considered because they are difficult to identify by routine staining and culture techniques.\textsuperscript{8}

\textit{Klebsiella pneumoniae} is the number 1 pathogen found in pyogenic liver abscesses in Taiwan and Korea and usually occurs in a monobacterial, as opposed to mixed bacterial, setting. Investigation into the K antigen serotype revealed that the K1 serotype accounts for 60\% of \textit{K pneumoniae} strains causing liver abscess in these countries. In contrast, this particular serotype is rarely found in clinical isolates from Western countries. In Taiwan and Korea, the average age to develop a \textit{K pneumoniae} liver abscess is 55 to 60 years. These abscesses are twice as likely to be diagnosed in men than in women and are much more likely to be cryptogenic in origin (64\%). Diabetes is a known risk factor for developing \textit{K pneumoniae} liver abscess and is a significant risk factor for embolic complications, especially endophthalmitis.\textsuperscript{17,18}

\section*{Diagnosis}

The clinical presentation of pyogenic liver abscess is usually subacute and nonspecific, leading to delays in presentation, diagnosis, and treatment. In Seeto and Rocky’s review\textsuperscript{11} of 142 patients with pyogenic liver abscesses, the classic triad of fever, jaundice, and right upper quadrant tenderness was present in less than 10\% of patients overall.

\section*{Clinical Presentation}

Most patients have fever (92\%), and 50\% have abdominal pain, but only half have pain in the right upper quadrant. Diarrhea occurs in less than 10\% of patients. The liver may be tender (65\%) and enlarged (48\%), and the patient may appear jaundiced (54\%). Other nonspecific complaints include malaise, anorexia, and nausea. If the diaphragm is involved, pleuritic chest pain, cough, or dyspnea may occur. If the abscess ruptures, peritonitis and sepsis may be presenting features\textsuperscript{7,9,11} (Table 56-4).

\begin{table}[h]
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\begin{tabular}{|l|l|}
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\textbf{TABLE 56-4: SYMPTOMS, SIGNS, AND LABORATORY DATA OF PYOGENIC LIVER ABSCESSES} \\
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\end{table}
Laboratory Evaluation

Leukocytosis is present in 70% to 90%, an elevated alkaline phosphatase in 80%, and an elevated bilirubin and transaminases in 50% to 67% of patients. Anemia, hypoalbuminemia, and prolonged prothrombin time are seen in 60%
Radiology

Plain films such as chest radiographs are abnormal in 50% of patients. Findings may include an elevated right hemidiaphragm, a right pleural effusion, and/or right lower lobe atelectasis. Abdominal films may show hepatomegaly, air-fluid levels in the presence of gas-forming organisms, or portal venous gas if pylephlebitis is the source (Fig. 56-2). Ultrasound will distinguish solid from cystic lesions and is cost-effective and portable. Ultrasound (US) is 80% to 95% sensitive but has limited utility in the morbidly obese and in lesions that are located under the ribs or located in an inhomogeneous liver.

Computed tomography (CT) is more sensitive (95%-100%) than US in detecting hepatic abscesses. On CT examination, an abscess is of lower attenuation than the surrounding liver, and the wall of the abscess may enhance with intravenous contrast administration. Lesions are detectable to around 0.5 cm with CT and are not limited by shadowing from ribs or air. CT and US may be used to evaluate and potentially treat the source of infection by percutaneous drainage (Figs 56-3 and 56-4). Radionuclide scanning with technetium-99m is no longer used and has been completely replaced by CT and US. However, cholangiography, usually through an indwelling biliary stent, may visualize the abscess (Fig. 56-5).
FIGURE 56-3  A. Abdominal ultrasound demonstrating a pyogenic liver abscess. The lesion appears as a low-density collection with small internal echos. B. Duplex ultrasound of pyogenic liver abscess with intervening portal vessels blocking safe access to percutaneous drainage.
FIGURE 56-4  A. Abdominal CT demonstrating a large pyogenic abscess that is of low density. B. Percutaneous drainage of posterior liver abscess. C. MRI of liver abscesses. CT, computed tomography; MRI, magnetic resonance imaging.
FIGURE 56-5 Cholangiogram via a transhepatic stent in a patient with biliary obstruction secondary to recurrent gastric cancer. It shows a communicating liver abscess.

**Treatment**

The appropriate treatment for pyogenic liver abscesses requires treatment of the abscess itself and concomitant treatment of the source. Drainage of a pyogenic abscess is essential for cure in most cases. Although antibiotics alone may be curative, these patients have a higher risk of failure and complications such as abscess rupture. Percutaneous transhepatic drainage is
a relatively low-risk and successful treatment method for both polymicrobial liver abscesses and *K pneumoniae* liver abscesses.\textsuperscript{17} Steps in management include antibiotic administration, radiologic confirmation by US or CT, and drainage. Exceptions to this strategy include multiple small abscesses and miliary fungal abscesses. These abscesses are treated with intravenous antibiotics and antifungals, respectively, without a drainage procedure.

**ANTIBIOTICS**

After confirmatory imaging with US or CT, abscesses are aspirated, blood cultures are drawn, and broad-spectrum intravenous antibiotics are administered until sensitivities allow a more selective antibiotic choice. Serologic testing also should be performed if an amebic abscess is suspected.\textsuperscript{9}

Classic antibiotic regimens include an aminoglycoside, clindamycin, and either ampicillin or vancomycin. However, *E coli, K pneumoniae*, and other Enterobacteriaceae have developed up to 30% resistance to these antibiotics. Fluoroquinolones can replace aminoglycosides, and metronidazole can be used instead of clindamycin, especially if an amebic source is suspected. Single-agent therapy with ticarcillin-clavulanate, imipenem-cilastatin, or piperacillin-tazobactam also is acceptable.\textsuperscript{12} Recent reports advise a third-generation cephalosporin and metronidazole or piperacillin-tazobactam as the initial regimen of choice. Carbapenems are recommended when extended-spectrum β-lactamase–producing strains are isolated. Treatment used to be given for 4 to 6 weeks; however, many studies now document success with only 2 weeks of antibiotic therapy.\textsuperscript{8} Empiric antibiotics should include anaerobic coverage in older pyogenic liver abscess patients, particularly in the setting of malignancy.\textsuperscript{16}

For patients with a *K pneumoniae* liver abscess, ampicillin alone is not recommended. In addition, metronidazole is ineffective against aerobic organisms, and regimens containing first-generation cephalosporins have been shown to be inferior in treatment of *K pneumoniae* liver abscess. Thus, a broad-spectrum penicillin, such as piperacillin-tazobactam, or a second- or third-generation cephalosporin is preferred for patients with *K pneumoniae* liver abscess.\textsuperscript{17}

Antibiotics alone have an 80% success rate for solitary abscesses with a
diameter <5 cm. In a series of 107 patients with unilocular hepatic abscesses of <3 cm, treatment with antibiotics alone had a 100% success rate. In the setting of multiple abscesses <1.5 cm in size and no concurrent surgical disease, patients may be treated with intravenous antibiotics alone. However, multiple small abscesses frequently imply biliary tract disease and may require biliary drainage for source control. Similarly, fungal abscesses are miliary in nature and not amenable to percutaneous or surgical drainage.

**ANTIFUNGALS**

Candidal liver abscess is a rare disease reported most commonly in patients with hematologic malignancies during periods of neutropenia resolution. Most of the candidal liver abscesses in patients with hematologic malignancies are a manifestation of disseminated candidiasis and have high mortality rates. They also can be acquired by fungemia from the portal vein or an ascending retrograde infection from the biliary tree. In patients with hematologic malignancies, the yield of positive culture is often less than 50%, with the diagnosis usually based on microscopic examination or histopathology from deep tissues. Higher doses of amphotericin B (2-9 g) are recommended by most experts because a cumulative dose of <2 g correlated with residual lesions at autopsy. Cases of hepatosplenic candidiasis have been successfully treated with fluconazole. Symptoms improved at 3 to 8 weeks, but resolution of the lesions on CT scan was noted after at least 1 month of fluconazole.20

*Candida glabrata* often has reduced susceptibility to both azoles and amphotericin B, and opinions on best therapy are divided. Both *Candida krusei* and *C glabrata* appear susceptible to caspofungin, and this agent may be a good alternative. Although fungemia due to *C glabrata* has been treated successfully with fluconazole (6 mg/kg/d), many experts prefer amphotericin B deoxycholate (>0.7 mg/kg/d). On the basis of pharmacokinetics predictions, fluconazole (12 mg/kg/d; 800 mg/d for the 70-kg patient) may be a suitable alternative, particularly in less critically ill patients.21

**ASPIRATION AND PERCUTANEOUS CATHETER DRAINAGE**

Needle aspiration and percutaneous catheter drainage of liver abscesses have
similar mortality rates; however, recurrence rates and the requirement for surgical intervention may be greater in those who undergo aspiration alone. Needle aspiration is less invasive, less expensive, and avoids all of the complications associated with catheter care. Giorgio and colleagues reported a series of 115 patients with a 98.3% success rate for needle aspiration, no mortality, and no procedure-related morbidity. A randomized controlled trial by Rajak et al in 1998 compared percutaneous needle aspiration to catheter drainage and also found no major complications and no deaths. They did, however, report only 60% success with needle aspiration versus a 100% success rate with catheter drainage. The highest rate of recurrence (15%) occurred in patients with biliary tract disease and obstructive lesions, whereas the recurrence rate with cryptogenic abscesses was less than 2%. This observation suggests that the underlying lesion should influence the type of therapy chosen. Another option that is infrequently employed is repeated aspiration.

Patients in whom percutaneous drainage is not appropriate include those with (1) multiple large abscesses; (2) a known intra-abdominal source that requires surgery; (3) an abscess of unknown etiology; (4) ascites; and (5) abscesses that would require transpleural drainage. An example of a patient managed by percutaneous drainage is provided in Figure 56-6.
FIGURE 56-6  A. CT demonstrating a pyogenic abscess in the right hepatic lobe. B. Contrast injected into the abscess cavity through a percutaneously placed drainage catheter. C. Sinogram performed 2 weeks later revealing a decrease in the size of the abscess cavity. D. CT after 4 weeks demonstrating complete resolution of the abscess. CT, computed tomography. (Reproduced with permission from Zuidema GD: Shackleford’s Surgery of the Alimentary Tract, 4th ed. Philadelphia, PA: WB Saunders; 1996.)
SURGICAL DRAINAGE

Surgical drainage was the widely accepted treatment for liver abscesses for many years following Ochsner’s 1938 report. Right-sided abscesses were drained extraperitoneally via a 12th rib resection to avoid contamination of the peritoneal cavity. With the advent of systemic antibiotics, transperitoneal surgical exploration also was considered a safe surgical approach. Advantages of the transperitoneal approach include the ability to: (1) treat the inciting pathology in the remainder of the abdomen/pelvis; (2) gain access and exposure of the entire liver for evaluation and treatment; and (3) access the biliary tree for cholangiography and bile duct exploration.

Since the 1980s, treatment has shifted to a less invasive approach utilizing percutaneous needle aspiration or catheter drainage to treat pyogenic abscesses. Surgical drainage is currently reserved for patients who have failed nonoperative therapy, those who need surgical treatment of the underlying source, those with multiple macroscopic abscesses, those on steroids, or those patients with concomitant ascites.

Complications

Up to 40% of patients develop complications from pyogenic liver abscesses, with the most common being generalized sepsis. In addition to sepsis, morbidity can include pleural effusions, empyema, and pneumonia. Abscesses also may rupture intraperitoneally, which is frequently fatal. Usually, however, the abscess does not rupture, but develops a controlled leak resulting in a perihepatic abscess. Pyogenic abscesses also may cause hemobilia and hepatic vein thrombosis.

Bacteremia is extremely common (95%) in *K pneumoniae* liver abscesses as opposed to other types of pyogenic liver abscesses (50%). As a result, end-organ seeding and distant abscesses are common. Extrahepatic abscesses occur in 7% to 12% of patient with *K pneumoniae* liver abscesses, with the most commonly reported organ being the eye. Endophthalmitis occurs in to 6% to 61% of cases and commonly occurs after liver abscess drainage. Disseminated intravascular coagulation, septic pulmonary emboli, and acute renal failure are also well-documented complications of *K pneumoniae* liver abscess.
Outcome

Between the 1950s and 1990, mortality rates varied from as low as 11% to as high as 88%. High mortality rates came from delay or failure to diagnose the abscess, failure to detect smaller intrahepatic abscesses, ineffective surgical drainage, lack of source control, associated malignancy, immune insufficiency, or other major comorbid conditions. No general consensus has been reached regarding risk factors due to the variability of the patient population being studied (Table 56-5).

**TABLE 56-5: FACTORS ASSOCIATED WITH A POOR OUTCOME IN PATIENTS WITH PYOGENIC LIVER ABSCESSES**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 years</td>
<td>WBC count &gt;20,000/µL</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increasing bilirubin</td>
</tr>
<tr>
<td>Associated malignancy</td>
<td>Increasing aspartate aminotransferase</td>
</tr>
<tr>
<td>Biliary etiology</td>
<td>Albumin &lt;2 g/dL</td>
</tr>
<tr>
<td>Multiple abscesses</td>
<td>Aerobic abscess</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Significant complication</td>
</tr>
<tr>
<td>Polymicrobial bacteremia</td>
<td></td>
</tr>
</tbody>
</table>

 Abbreviation: WBC, white blood cell.

The prognosis for *K pneumonias* is better than for other pyogenic liver abscesses with respect to mortality (6%-17%) and disease relapse. Prognosticators for mortality in *K pneumonias* liver abscess are abscess >5 cm, concomitant sepsis, intrahepatic gas formation, APACHE III score >40, delayed/inadequate abscess drainage, use of antimicrobials alone, thrombocytopenia, and diabetes. The main concern in this type of liver abscess is no longer mortality, but catastrophic disability due to irreversible ocular or neurologic complications. The *K pneumonias* genotype K1 is a pathogen capable of causing septic ocular or central nervous system complications from pyogenic liver abscess independent of host underlying diseases. The outcome for patients who develop endophthalmitis is grim because despite rapid intervention, visual acuity outcome is poor.
AMEBIC LIVER ABSCESS

Amebic liver abscess is caused by the parasitic protozoan *Entamoeba histolytica*. The disease was described in association with blood and mucus diarrheal stools in the 5th century BC by Hippocrates and other practitioners. In 1890, Sir William Osier described the first North American case when, after an attack of dysentery while in Panama, a physician’s stool and abscess fluid were both found to contain amebae. Councilman and LaFleur of Johns Hopkins Hospital went on to detail the pathogenic role of amebae and coined the terms “amebic dysentery” and “amebic liver abscess” in 1891. Amebic liver abscess is the most common extraintestinal form of invasive amebiasis, and an estimated 100,000 people succumb to this disease each year.

Etiology

Three species of ameba mainly infect humans. *Entamoeba dispar* is associated with an asymptomatic carrier state and not with disease. *Entamoeba moshkovskii* has been associated with mild gastrointestinal discomfort. *E histolytica* is responsible for all forms of invasive disease. The life cycle involves cysts, invasive trophozoites, and fecally contaminated food or water to initiate the infection. Fecal-oral transmission occurs; the cyst passes through the stomach into the intestine unscathed, and pancreatic enzymes start to digest the outer cyst wall. The trophozoite is then released into the intestine and multiplies there. Normally, no invasion occurs, and the patient develops amebic dysentery or becomes an asymptomatic carrier. In a small number of cases, the trophozoite invades through the intestinal mucosa, travels through the mesenteric lymphatics and veins, and begins to accumulate in the hepatic parenchyma, forming an abscess cavity. Liquefied hepatic parenchyma with blood and debris gives a characteristic “anchovy paste” appearance to the abscess.

Incidence

Worldwide, an estimated 500 million people are carriers of *E histolytica* or *E dispar*, 50 million people have active disease, and 50,000 to 100,000 die annually. The vast majority of these infections are acquired in the developing
world. Amebiasis is common in Africa, Indochina, and Central and South America. Up to 5% of diarrheal illness in Mexico is due to *Entamoeba* disease. The overall prevalence in the United States is 4% per year. High-risk groups in the United States include sexually active homosexual men, immigrants, tourists who travel to endemic areas, institutionalized people, and those with HIV. Children also have been known to infect entire families. Amebiasis follows a bimodal age distribution. One peak is at age 2 to 3 years, with a case-fatality rate of 20%, and the second peak is at >40 years, with a case-fatality rate of 70%. Those living in developing countries have a greater risk and an earlier age of infection than do those in developed regions. Low socioeconomic status and unsanitary conditions are significant independent risk factors for infection. Amebic liver abscess is 10 times as common in men as in women and is a rare disease in children. The reason for this vast difference between the sexes is not clear. Greater alcohol consumption among men, which may impair Kupffer cellular function as well as cellular and humoral immune response, and the potentially protective effects of hormones and iron deficiency anemia in menstruating women have been proposed to play a role.

**Pathology**

Roughly 90% of people who become infected with *E histolytica* are asymptptomatically colonized, and factors that control the invasiveness of this organism are not completely understood. *E histolytica* cysts can last for days in a dried state at temperatures of 30°C. These cysts are resistant to the effects of gastric acid pH, but become stimulated to form trophozoites in the alkaline pH of the bowel. Trophozoites are found in the colon and in the feces of humans and mammals. Humans become reservoirs, and transmission occurs by ingesting food and water contaminated with amebic cysts, or occasionally through person-to-person contact. Incubation takes 1 to 4 weeks. Left untreated, asymptomatic individuals may shed cysts for many years.

The reasons why only a small portion of the colonized people will develop invasive disease are not fully understood. Virulence factors of the parasite (eg, the amount of secreted cysteine proteinases, phospholipases, hemolysins, and amebapores) and the host’s immune status are the most likely factors. Invasive amebiasis can include anything from amebic dysentery to metastatic
abscesses. The most common form of the invasive disease is colitis. The majority (70%-80%) of patients experience a gradual onset of symptoms with worsening diarrhea, abdominal pain, weight loss, and stools containing blood and mucus. Trophozoites invade and induce apoptosis in colonic mucosa, resulting in “buttonhole” ulcers with undermined edges. Trophozoites are actually found in the edge of the ulcers.

The most common extraintestinal site of amebiasis is the liver, occurring in 1% to 7% of children and 50% of adults (usually males) with invasive disease. Trophozoites reach the liver through the portal system, causing focal necrosis of hepatocytes and multiple microabscesses that coalesce into a single abscess. The central cavity of the lesion contains a homogenous thick liquid that is typically red/brown and yellow in color and similar to anchovy paste in consistency.

Diagnosis

The definitive diagnosis of amebic liver abscess is by detection of *E. histolytica* trophozoites in the pus and by finding serum antibodies to the ameba. The differential diagnosis should include pyogenic liver abscess, necrotic adenoma, and echinococcal cyst.

CLINICAL PRESENTATION

Ninety percent of amebic liver abscesses occur in young adult males. The presentation may be acute, with fever and right upper quadrant (RUQ) pain, or subacute, with weight loss and, less frequently, fever and abdominal pain. The usual case of amebic liver abscess does not present with concurrent colitis, but patients may have had dysentery within the past year. Alcohol abuse is common. Eighty percent of patients with amebic liver abscess present with symptoms that develop within 2 to 4 weeks, including fever, cough, and a dull aching pain in the RUQ or epigastrium. Diaphragmatic involvement causes right-sided pleural pain or pain referred to the shoulder. Gastrointestinal symptoms of nausea, vomiting, abdominal cramping, abdominal distention, diarrhea, and constipation occur in 10% to 35%. Hepatomegaly with point tenderness over the liver or subcostal region is common (Table 56-6). In contrast to pyogenic liver abscesses, amebic liver
abscesses are more likely to occur in males under 50 years old who have immigrated or traveled to a country where the disease is endemic. The patient also will not be jaundiced or have biliary disease or diabetes mellitus\(^{27}\) (Table 56-7).

**TABLE 56-6: SYMPTOMS, SIGNS, AND LABORATORY DATA OF AMEBIC LIVER ABSCESSES**
<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of Amebic Abscesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>90</td>
</tr>
<tr>
<td>Fever</td>
<td>87</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>85</td>
</tr>
<tr>
<td>Anorexia</td>
<td>50</td>
</tr>
<tr>
<td>Weight loss</td>
<td>45</td>
</tr>
<tr>
<td>Malaise</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
</tr>
<tr>
<td>Cough or pleurisy</td>
<td>25</td>
</tr>
<tr>
<td>Pruritus</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

**Sign**

<table>
<thead>
<tr>
<th>Sign</th>
<th>% of Amebic Abscesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>85</td>
</tr>
<tr>
<td>Right upper quadrant tenderness</td>
<td>84</td>
</tr>
<tr>
<td>Pleural effusion or rub</td>
<td>40</td>
</tr>
<tr>
<td>Right upper quadrant mass</td>
<td>12</td>
</tr>
<tr>
<td>Ascites</td>
<td>10</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5</td>
</tr>
</tbody>
</table>

**Laboratory data**

<table>
<thead>
<tr>
<th>Laboratory data</th>
<th>% of Amebic Abscesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased alkaline phosphatase</td>
<td>80</td>
</tr>
<tr>
<td>WBC count &gt;10,000/μL</td>
<td>70</td>
</tr>
<tr>
<td>Hematocrit &lt;36%</td>
<td>49</td>
</tr>
<tr>
<td>Albumin &lt;3 g/dL</td>
<td>44</td>
</tr>
<tr>
<td>Bilirubin &gt;2 mg/dL</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviation: WBC, white blood cell.
LABORATORY EVALUATION

Patients may present with a mild to moderate elevation of the white blood cell count and anemia. Acutely, alkaline phosphatase will be normal and alanine aminotransferase levels will be elevated. The opposite is true in patients with chronic disease. Jaundice is rare. Because amebic abscesses involve destruction of liver parenchyma and are often larger than pyogenic liver abscesses, patients may have an elevated prothrombin time. If colitis is present, wet mount preps of stool samples contain trophozoites 30% of the time in 1 sample and 70% of the time if 3 samples are tested. Patients with an amebic liver abscess have positive stool samples in 40% to 50% of cases.

RADIOLOGY

Chest radiographs are abnormal in two-thirds of patients with amebic liver abscess and frequently show pleural effusion, infiltrates, or an elevated hemidiaphragm. US, CT, and magnetic resonance imaging (MRI) are all excellent methods for detecting amebic liver abscesses but are nonspecific. In 75% to 80% of cases, only a single abscess is present and located in the right lobe. Ten percent are in the left lobe, and the rest are multiple. Six percent may present as a caudate lobe abscess. Only 40% have typical sonographic features of amebic liver abscess, and serial scanning shows no change in the US features despite adequate treatment. The mean time to resolution is 7 months, and 70% have findings that persist for more than 6 months. Eventually, resolution may be complete or result in a small residual

<table>
<thead>
<tr>
<th>Amebic</th>
<th>Pyogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 years</td>
<td>Age &gt;50 years</td>
</tr>
<tr>
<td>Male-to-female ratio 10:1</td>
<td>Male-to-female ratio 1:1</td>
</tr>
<tr>
<td>Hispanic descent</td>
<td>No ethnic predisposition</td>
</tr>
<tr>
<td>Recent travel to endemic area</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Pulmonary dysfunction</td>
<td>High fevers</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>Septic shock</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Palpable mass</td>
</tr>
</tbody>
</table>
cystic cavity that resembles a simple cyst of the liver.31

SEROLOGY

Serum antibodies are positive in 85% of patients with invasive colitis and 99% of patients with liver abscesses.32 Countries with a high prevalence of amebiasis also have a high prevalence of positive serologies in asymptomatic individuals. Therefore, serologies help exclude the diagnosis only in appropriately chosen populations. Patients with E dispar infection will have negative serologies. Biopsies of the edge of an ulcer or the wall of an abscess reveal trophozoites with periodic acid-Schiff stain.26

DIAGNOSTIC ASPIRATION

Serologic data are usually available within 24 to 48 hours; therefore, the need to aspirate a suspected amebic abscess is questionable. Diagnostic aspirations usually are done when amebic serologies are negative and a pyogenic cause needs to be ruled out. The fluid of an amebic abscess is odorless, and Gram stain and cultures are negative. Amebae are recovered in 33% to 90% of aspirates, and wall scrapings increase the yield. Aspiration should not be done if an echinococcal cyst or a cancer is suspected. The former may result in anaphylactic shock, and the latter has the potential to seed the tract with malignant cells.8

The diagnosis of invasive amebiasis is most commonly attempted by a combination of stool testing for ova and parasites (O&P) and serologic testing, possibly coupled with colonoscopy and biopsy of intestinal lesions or drainage of liver abscesses. Numerous studies have demonstrated the inadequacies of microscopic examination for E histolytica for the diagnosis of both amebic colitis and liver abscess. Antigen detection or polymerase chain reaction (PCR) to detect E histolytica in the stool is a better approach than O&P, but requires fresh or frozen stool specimens (versus preserved), and PCR is impractical in the developing world. The detection of amebic markers in the sera of patients with amebic colitis and liver abscess remains only a research tool.28

Treatment
Since the introduction of metronidazole in the 1960s, surgical drainage of amebic liver abscesses has become virtually unnecessary. Drainage procedures, regardless of the approach, are reserved for patients in whom the diagnosis is questionable or when complications occur.

**ANTIBIOTICS**

Noninvasive infections can be treated with paromomycin. Nitroimidazoles, especially metronidazole, are the mainstays of treatment for invasive amebiasis. Nitroimidazoles with longer half-lives (secnidazole, tinidazole, and ornidazole) are better tolerated and can be given for shorter periods of time but are not available in the United States. Metronidazole reaches high concentrations in the liver, stomach, intestine, and kidney. This antibiotic crosses the placenta and blood-brain barrier and is contraindicated in the first trimester of pregnancy. The drug also is excreted in milk; thus, breastfeeding should be discontinued during use. Serious side effects are rare. Positive responses to metronidazole should be seen by the third day of treatment. At 5 days, an 85% cure rate is achieved, and this response may be increased to 95% by 10 days. Five to 15% of patients with amebic liver abscess may be resistant to metronidazole. Parasites persist in the intestine in up to 40% to 60% of patients who receive a nitroimidazole; thus, nitroimidazole treatment should be followed with paromomycin or diloxanide furoate to cure luminal infection or risk relapse from residual infection in the intestine. Chloroquine also is effective and has an excellent dose distribution in the liver. Chloroquine use is recommended as an adjunct to standard antimicrobial therapy in cases of large or multiple abscesses.

In summary, amebic liver abscess is usually managed by the administration of metronidazole or tinidazole, followed by treatment with a luminal amebicide (paromomycin or diloxanide furoate).

**THERAPEUTIC ASPIRATION**

Blessmann and colleagues reported a prospective, randomized trial of patients with amebic abscesses who were treated with metronidazole alone or with US-guided aspiration of the fluid plus medication. Fever, RUQ pain, liver tenderness, and laboratory studies such as erythrocyte sedimentation rate, white blood cell count, hemoglobin, C-reactive protein, and abscess size
were obtained on admission and daily thereafter. Abscess aspiration resulted in improved liver tenderness within the first 3 days, but no other difference was demonstrable between the 2 groups. The authors concluded that this minor benefit was insufficient to justify routine needle aspiration. They advocated drug treatment alone for uncomplicated abscesses with a diameter up to 10 cm and located in the right lobe of the liver. However, aspiration may be considered in patients with pleuropulmonary extension and in pregnancy when metronidazole is contraindicated.

Therapeutic aspiration may occasionally be required as an adjunct to antiparasitic treatment. Drainage should be considered in patients who have no clinical response to drug therapy within 5 to 7 days or those with a high risk of abscess rupture defined as having a cavity diameter >5 cm or lesions located in the left lobe. A 2009 Cochrane review attempted to lay to rest the controversy surrounding percutaneous needle aspiration of uncomplicated amebic liver abscesses. The authors found that percutaneous needle aspiration did not help patients with uncomplicated amebic liver abscess. Benefits were observed in resolution time of pain and tenderness, but no additional benefit was found with percutaneous needle aspiration plus metronidazole versus metronidazole alone for uncomplicated amebic liver abscesses. Bacterial coinfection of amebic liver abscess has been observed; therefore, addition of antibiotics, drainage, or a combination of both to nitroimidazole therapy may be necessary.

DRAINAGE

Percutaneous or surgical drainage should be reserved for cases in which the diagnosis of amebic liver abscess is in question or when complications occur.

**Percutaneous.** Image-guided percutaneous catheter drainage has replaced surgical intervention as the procedure of choice for decreasing the size of an abscess. Percutaneous drainage remains most useful for treating pulmonary, peritoneal, and pericardial complications. The high viscosity of amebic abscess fluid, however, requires a large-diameter catheter for adequate drainage, and these catheters may cause more discomfort for the patient. Secondary infections related to the indwelling catheter are always a risk of this intervention.
Surgical. Surgical drainage of amebic liver abscesses has largely been replaced by antibiotic therapy. The most common indication for surgical intervention is to manage abscesses that have failed to respond to more conservative therapy. Laparotomy is indicated for life-threatening hemorrhage that may or may not be related to abscess rupture, or when the amebic abscess erodes into a neighboring viscus and control of the involved viscus is necessary. Sepsis due to a secondarily infected amebic abscess also warrants operative intervention if percutaneous treatment fails.\(^8\)

**Complications**

Complications from amebic abscesses occur secondary to rupture of the abscess into the peritoneum, pleural cavity, or pericardium (Fig. 56-7). Extrahepatic sites also have been described in the lung, brain, skin, and genitourinary tract, presumably from hematogenous spread.\(^27\) Ruptured amebic liver abscesses occur in 2% to 17% of patients and are associated with mortality rates between 12% and 50%.\(^31\)
Peritonitis associated with amebiasis is due to rupture in the majority (78%) of cases and, less commonly, secondary to necrotizing or perforated amebic colitis (22%). The liver abscess usually adheres to the diaphragm and the anterior abdominal wall, or the omentum and bowel tend to wall it off. Rupture into the colon or stomach also may occur. Free rupture into the peritoneal cavity is uncommon and occurs in moribund patients or those with poor nutrition.\textsuperscript{31}

Thoracic amebiasis (empyema, bronchohepatic fistulas, and pleuropulmonary abscess) is the most common complication, followed by
pericardial amebiasis (acute pericarditis with tamponade). Transdiaphragmatic involvement manifests as dyspnea and dry cough. On exam, right basilar crackles and a pleural rub may be heard. Plain films show atelectasis and blunting of the costophrenic angle. If the abscess ruptures into the pleural cavity, it usually occurs suddenly, collapsing the lung, filling up the pleural space, and whiting out the lung on chest x-ray. Treatment requires drainage of the pleural cavity with tube thoracostomy. If the abscess ruptures into the bronchi, this complication causes sudden onset of coughing with expectoration of copious brown sputum. Surgical intervention is not required, as the abscess is usually walled off from the pleural and peritoneal cavities. Postural drainage, bronchodilators, and antiamebic drugs may suffice.

Left lobe abscesses are more likely to involve the pericardium. Complications range from asymptomatic effusions, to cardiac tamponade, to intrapericardial rupture. If pericardial thickening or effusion is noted on imaging, some experts believe that this is an indication for aspiration of a left lobe liver abscess. When tamponade develops, aspiration of the pericardium, drainage of the liver abscess, and antiamebic drugs are indicated. Cerebral amebiasis is seen in up to 8% of autopsies. These patients are severely ill from sepsis and may experience seizures.

Outcome

The majority of patients with amebic liver abscess defervesce within 3 to 4 days of treatment, however, left untreated, amebic liver abscesses may be fatal. Mortality rates of 0% to 18% are reported, with higher rates occurring secondary to a delay in diagnosis, or when secondary bacterial infection or complications (abscess rupture) occur. Independent risk factors for mortality include serum bilirubin >3.5 mg/dL, encephalopathy, hypoalbuminemia defined as <2.0 g/dL, and the presence of multiple abscess cavities. Abscess aspiration is a risk factor for secondary bacterial infection; however, in recent reports, secondary bacterial infection rates have decreased from 10% to 20% to 0% to 4% (Table 56-8).

| TABLE 56-8: FACTORS ASSOCIATED WITH A POOR OUTCOME IN PATIENTS WITH AMEBIC LIVER ABSCESSES |
Increased age
Increased bilirubin level
Pulmonary involvement
Rupture or extension
Late presentation

HYDATID LIVER CYST

Echinococcosis (hydatid disease) is a zoonosis caused by the larval stage of *Echinococcus granulosus* (also known as *Taenia echinococcus*). Humans are accidental intermediate hosts, whereas animals can be both intermediate and definitive hosts. The 2 main types of hydatid disease are caused by *E. granulosus* and *Echinococcus multilocularis*. The former is commonly seen in the Mediterranean, South America, the Middle East, Australia, and New Zealand, and is the most common type of hydatid disease. In humans, 50% to 75% of the cysts occur in the liver, 25% are located in the lungs, and 5% to 10% distribute along the arterial system. Infection with echinococcal organisms is the most common cause of liver cysts in the world.

**Etiology**

The life cycle of *E. granulosus* has 2 hosts. The definitive host is usually a dog or some other carnivore. The adult worm of the parasite lives in the proximal small bowel of the definitive host attached by hooklets to the mucosa. Eggs are released into the host’s intestine and excreted in the feces. Sheep are the most common intermediate host, and these animals ingest the ovum while grazing. The ovum loses the protective chitinous layer and is digested in the duodenum. The released hexacanth embryo (oncosphere) passes through the intestinal wall into the portal circulation and develops into cysts within the liver. The definitive host eats the viscera of the intermediate host to complete the cycle (Fig. 56-8).
Humans may become intermediate hosts through contact with the definitive host (usually a dog) or by ingestion of contaminated water or vegetables. Once in the liver, cysts grow to 1 cm in the first 6 months and 2 to 3 cm annually thereafter. Once the parasite passes through the intestinal wall into the portal venous or lymphatic system, the liver is the first line of defense, and thus is the most frequently involved organ.
Incidence

The incidence of hydatid liver cysts in the United States is approximately 200 cases per year, with an increased frequency in immigrant populations. Hydatid liver disease affects all age groups and both sexes equally, and no predisposing pathologic conditions are associated with infection. Public education about the life cycle and transmission of the disease has helped decrease the incidence. Washing hands after contact with canines, eliminating the consumption of vegetables grown at ground level from the diet, and stopping the practice of feeding entrails of slaughtered animals to dogs have all aided in decreasing the incidence of the disease.8

Pathology

Hydatid liver cysts tend to expand slowly and without symptoms and are thus frequently very large on presentation. Single lesions are noted in 75% of patients and are predominantly located within the right lobe (80%).37 Even though the lesion is single, half contain daughter cysts and are multilocular.

The typical hydatid cyst has a 3-layer wall surrounding a fluid cavity. The outer layer is the pericyst, a thin, indistinct fibrous tissue layer representing an adventitial reaction to the parasitic infection. The pericyst acts as a mechanical support for the hydatid cyst and is the metabolic interface between the host and the parasite. As the cyst grows, bile ducts and blood vessels stretch and become incorporated within this structure. This process explains the biliary and hemorrhagic complications of cyst growth and difficulties with resection. Over time, the pericyst calcifies.8

The outer layer of the cyst itself is the ectocyst or laminated membrane and is bluish-white, gelatinous, and about 0.5 cm thick. This membrane is a cuticular chitinous structure without nuclei and acts as a barrier for bacteria and an ultrafilter for protein molecules.

The inner layer or endocyst is the germinal membrane, responsible for the production of clear hydatid fluid, the ectocyst, brood capsules, scoleces, and daughter cysts. The endocyst is 10 to 25 µm thick and attached tenuously to the laminated membrane. The absorptive function of the inner layer is important for cyst nutrition. The inner layer also has a proliferative function producing the ectocyst and scoleces.39 This germinal layer forms small
cellular masses that give rise to brood capsules, in which future worm heads develop. They enlarge and develop into invaginated protoscoleces with 4 suckers and a double row of hooks—a protoscolex. The protoscolex fully differentiates and matures attached by a pedicle to the capsule wall. Brood capsules and freed protoscoleces are released into the fluid of the original cyst and, together with calcareous bodies, form hydatid sand.

Hydatid sand is made up of around 400,000 scoleces per milliliter of fluid. The protoscolex can differentiate in 2 directions. In the definitive host, the scolex becomes an adult tapeworm. In the intermediate host, including humans, each of the released protoscoleces is capable of differentiating into a new hydatid cyst. Development of brood capsules from the germinal layer indicates complete biologic development of the cyst, which occurs after 6 months of growth.

Daughter cyst formation is a defense reaction. Hydatid cysts in humans are long-standing, large, and liable to injury. Any injury may cause daughter cyst formation. Daughter cysts are replicas of the mother cyst, and their size and number are variable. In uncomplicated cysts, the cyst cavity is filled with sterile, colorless, antigenic fluid containing salt, enzymes, proteins, and toxic substances. The formation of daughter cysts is called endogenic vesiculation.

Ectogenic vesiculation occurs when a small rupture or defect in the laminated membrane occurs and the germinal layer passes through and creates a satellite hydatid cyst. This process is uncommon in *E. granulosus*, but is characteristic for the larval stage of *E. multilocularis*. Because the liver parenchyma in humans cannot sequester *E. multilocularis* and the process of ectogenic vesiculation is fulminant, multiple vesicles are formed in all directions. The infected parenchyma has a multilocular appearance, and the center becomes necrotic, spongy, and filled with a gelatinous fluid similar to that of a mucoid liver carcinoma. Hepatic insufficiency is common, and the disease is often lethal.

**Diagnosis**

The diagnosis of uncomplicated hydatid liver cyst depends on the index of clinical suspicion. Most uncomplicated cysts are asymptomatic. Symptoms may arise due to a toxic reaction from the presence of the parasite or local
mechanical effects.

**CLINICAL PRESENTATION**

The clinical features of hydatid liver disease depend on the site, size, stage of development, whether the cyst is alive or dead, and whether the cyst is infected. Pain in the RUQ or epigastrium is the most common symptom, whereas hepatomegaly and a palpable mass are the most common signs. Nonspecific fever, fatigue, nausea, and dyspepsia may also be present (Table 56-9). Approximately one-third of patients will have eosinophilia, and only 20% will present with jaundice and hyperbilirubinemia.

| TABLE 56-9: SYMPTOMS, SIGNS, AND LABORATORY DATA OF HYDATID LIVER CYSTS |
|---------------------------------------------------------------|------------------|
| **Symptoms**                                                   | % of Hydatid Cysts |
| Asymptomatic                                                  | 75               |
| Abdominal pain                                                | 20               |
| Dyspepsia                                                     | 13               |
| Fever and chills                                              | 8                |
| Jaundice                                                      | 6                |
| **Signs**                                                      |                  |
| Right upper quadrant mass                                     | 70               |
| Right upper quadrant tenderness                                | 20               |
| **Laboratory data**                                           |                  |
| Eosinophilia                                                   | 35               |
| Bilirubin >2 mg/dL                                            | 20               |
| WBC count <10,000/μL                                          | 10               |

Abbreviation: WBC, white blood cell.

**SEROLOGY**
No single biochemical test definitively establishes the diagnosis. The Casoni and Weinberg tests are no longer used due to their low sensitivities. Determination of specific antigens and immune complexes of the cyst with enzyme-linked immunosorbent assay (ELISA) gives a positive result in more than 90% of patients. Specific IgE antibodies are demonstrated with ELISA and radioallergosorbent test (RAST) if active disease is present. The arc 5 antibody test involves precipitation during immunoelectrophoresis of the blood of patients with the antigen. Positivity for this test is 91%. Sbihi and colleagues reported that purified fractions enriched in antigens 5 and B and glycoproteins from hydatid fluid yielded a sensitivity of 95% with a specificity of 100%.

RADIOLOGY

Chest radiographs may show an elevated diaphragm and concentric calcifications in the cyst wall but are of limited value. US and CT are considered the first choice for imaging (Fig. 56-9). Classic findings of hydatid cysts are calcified thick walls, often with daughter cysts. US defines the internal structure, number, and location of the cysts and the presence of complications. The specificity of US in hydatid disease is around 90%. The classification proposed by Gharbi and associates provides a morphologic description. Type I has a pure fluid collection. Type II has a fluid collection with a split wall (floating membrane). Type III reveals a fluid collection with septa (honeycomb image). Type IV has heterogenous echographic patterns, and type V has reflecting thick walls. An updated classification system has been proposed by the World Health Organization (Table 56-10). Differential imaging characteristics of hepatic cysts are presented in Table 56-11.
FIGURE 56-9  A. CT scan demonstrating rupture of hydatid cyst through the diaphragm *(arrow)* into the pleural space. B. CT scan in the same patient demonstrating a heavily calcified hydatid cyst *(arrow)* with diaphragmatic penetration and a lightly calcified cyst on the left. C. CT scan in the same patient showing a third calcified cyst near the gallbladder fossa and a small superficial fourth cyst on the left. D. Endoscopic retrograde cholangiopancreatography in the same patient demonstrating biliary communication in the cyst that also penetrates the diaphragm. CT, computed tomography.
CT gives similar information to US, but more specific information about the location and depth of the cyst within the liver. Daughter cysts and exogenous cysts also are clearly visualized, and cyst volume can be
estimated. CT is imperative for operative management, especially when a laparoscopic approach is used.\textsuperscript{40} MRI provides structural details of the hydatid cyst, but adds little more than US or CT and is more expensive. Magnetic resonance cholangiopancreatography (MRCP) may show communication with the biliary system as well as provide detailed information on the biliary anatomy. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiogram (PTC) may show communication between the cysts and bile ducts and can be used to drain the biliary tree before surgery. The routine use of ERCP is advocated by some to completely define the bile duct anatomy and to visualize any clinically silent connections between the bile ducts and cysts.\textsuperscript{42}

**Treatment**

Most echinococcal cysts are asymptomatic on presentation, but potential complications such as pulmonary infection, cholangitis, rupture, and anaphylaxis give good reason to consider treatment for all. Medical, surgical, and percutaneous approaches may be part of the treatment armamentarium.\textsuperscript{42} Small cysts (<4 cm) located deep in the parenchyma of the liver, if uncomplicated, can be managed conservatively.\textsuperscript{40} Basic principles include: (1) eradication of the parasite within the cyst, (2) protection of the host against spillage of scoleces, and (3) management of complications.\textsuperscript{42}

**ANTIHELMINTHICS**

Medical therapy for echinococcosis is based on the benzimidazoles (mebendazole and albendazole) and, used alone, is only 30% successful. Albendazole is readily absorbed from the intestine and metabolized by the liver to an active form. Mebendazole is poorly absorbed and is inactivated by the liver. Albendazole is thus the drug of choice for medical therapy. Greater success rates may be observed in patients with extrahepatic manifestations of the disease and with the alveolar form caused by *E multilocularis*. Given for at least 3 months preoperatively, albendazole reduces the recurrence rate when cyst spillage, partial cyst removal, or biliary rupture has occurred. Duration of therapy in these instances is at least 1 month.\textsuperscript{42} Monitoring with
complete blood count and liver function tests throughout the duration of treatment is advised, as benzimidazoles are known to cause neutropenia and hepatotoxicity. Other side effects include nausea and occasionally alopecia. Pregnancy, chronic liver disease and myelosuppression are contraindications for their use. Combination therapy with praziquantel 40 mg/kg once weekly may be advisable in refractory disease.

PERCUTANEOUS ASPIRATION AND DRAINAGE

Historical surgical dictum stated that percutaneous puncture of a hydatid cyst is a dangerous and contraindicated activity. Potential risks including anaphylaxis, communication with the biliary tree, and spillage may outweigh possible advantages. In 1983, Fornage challenged this axiom and reported an accidental puncture of a hydatid cyst by US that had no clinical consequences. Many successful reports followed thereafter. The most frequently used protoscolecidal agents used for percutaneous treatment are 15% to 20% saline, 95% ethanol, a combination of 30% saline and 95% ethanol, and mebendazole solution.

PAIR technique stands for: puncture of the cyst wall, aspiration of cyst content, injection, and reaspiration of a scolecidal agent. PAIR involves initial puncture of the cyst under US or CT guidance, aspiration of cyst content, injection of contrast material to opacify the cyst, and infusion of scolecidal drug, followed by povidone-iodine infusion. The catheter stays clamped for 30 minutes, then povidone-iodine is infused again. The catheter is preserved for drainage. Except in the case of povidone-iodine infusion, aspiration can be followed by sclerotherapy or infusion of alcohol or a scolecidal such as albendazole. Recently, a modified PAIR technique was created to introduce concomitant evacuation of cyst contents while infusing scolecidal agent via a specially designed coaxial catheter system. The simultaneous aspiration/infusion process allows almost complete washout of cyst content, reducing chances of any scolices surviving, and maintenance of the intracystic pressure minimizes risk of biliary fistula formation. The PAIR technique has been combined with albendazole therapy with 70% success rates and a low rate of recurrence. In 1997, Filice and Brunetti reported a series of 163 patients with 231 cysts treated percutaneously. No complications were reported, and long-term results were good.

Indications for percutaneous treatment of liver hydatid cysts are type I and
II cysts, type III and IV cysts with drainable material, suspected fluid collections, infected hydatid cysts, inoperable patients, pregnant women, and patients with multiple, disseminated, or symptomatic cysts. Contraindications include subgroups of type III and IV cysts (hydatid cysts with heterogeneous echo pattern), liver cysts that have ruptured into the biliary system or peritoneum, cysts inaccessible to puncture, and children <3 years old. Type V cysts are not eligible for any intervention other than simple follow-up. Recurrence rates vary between 0% and 4%. Overall complication rates in percutaneous drainage range from 15% to 40%. Major complications (anaphylactic shock) are rare (0.1%-0.2%). Minor complications (urticaria, itching, hypotension, fever, infection, fistula, rupture into the biliary system) range from 10% to 30%. Cyst-biliary complications after PAIR and caused by cyst decompression can be handled endoscopically or by cyanoacrylate infusion. In one of the largest recently published series on the management of liver hydatid cysts, PAIR technique yielded good results in cystic lesions and cystic echinococcosis types 1 (CE1) and 2 (CE2) disease with low complication rates (1% biliary fistula, 1% abscess formation, 3.8% allergic reaction). Only 2.8% of patients required repeat procedure to achieve results.\textsuperscript{48} Cholangiography or ERCP is recommended before any attempt for percutaneous drainage to inject contrast material and make any communication visible. Overall mortality rates are as low as 0.1%.\textsuperscript{46}

\section*{Surgery}

Surgery remains the treatment of choice for uncomplicated hydatid disease of the liver, although much debate exists about the most appropriate surgical technique that can offer total extirpation of the parasites with minimal postoperative complications.\textsuperscript{46} The objectives of surgical treatment are to: (1) inactivate the scoleces, (2) prevent spillage of cyst contents, (3) eliminate all viable elements of the cyst, and (4) manage the residual cyst cavity. The surgical procedure varies from a radical resective open approach (pericystectomy or hepatic resection) to a conservative approach (drainage or obliteration of the cavity or both), which can potentially even be done laparoscopically\textsuperscript{40} (Fig. 56-10). One of the most important end points of hydatid cyst surgery may be recurrence. Dissemination of protoscolices-rich fluid during surgery and incomplete removal of the germinative membrane from the cyst cavity are major causes of recurrence (8.5%-25%) in
FIGURE 56-10  A. Open cyst evacuation demonstrating cyst aspiration (upper left), removal of daughter cysts (upper right), resection of active cyst lining (lower left), and packing with omentum (lower right). B. Pericystectomy demonstrating removal of a calcified pericyst (top right), closure of a small bile duct (middle left), and closure of the cavity over a drain (lower right). (Reproduced with permission from Cameron JL, Sandove C: Atlas of Surgery. Philadelphia, PA: BC Decker; 1990.)

Scolecidal Agents. Early on, surgical management of hydatid cysts via cyst evacuation resulted in a high rate of peritoneal implantation. This problem
prompted the use of scolecidal agents for injection into the cyst and for use in the surrounding peritoneum. Formalin, hypertonic saline, chlorhexidine, cetrimide, hydrogen peroxide, polyvinylpyrrolidone-iodine, silver nitrate, and ethyl alcohol are among some of the many agents that have been used.\textsuperscript{40,42,46} However, formalin caused sclerosing cholangitis when it entered the biliary tract. Hypertonic saline has to be used carefully to avoid biliary injection and hypernatremia. The safety of the other agents in the biliary tree has not been established. No agent should be injected pre-evacuation due to high intracyst pressure. The World Health Organization (WHO) regards the use of scolecidal agents for intraoperative killing of infectious material as questionable, because no agent is both effective and safe. According to WHO, ethanol (70%-95%), hypertonic saline (15%-20%), and cetrimide solution (0.5%) are deemed substances with relatively low risk.\textsuperscript{49} Chlorhexidine gluconate 0.04% (Chx-Glu) is relatively nontoxic, without harmful effects on the biliary tract, and is not affected by dilution in the cyst fluid. In addition, Chx-Glu is commonly available, easily prepared, and inexpensive and was 100% effective on protoscolices and the germinative membrane and may be the preferred scolecidal agent.\textsuperscript{49}

**Open Cyst Evacuation.** The safest surgical approach is open cyst evacuation. Peripherally located cysts are the most easily treated, and either abdominal or flank approaches may be used depending on cyst location. Prior to opening the cyst, the field is lined with hypertonic (20%) saline-soaked gauze to guard against spillage. The cyst is then opened, and the contents are aspirated with a suction device that is capable of generating high negative pressures. The cyst is then opened completely, and any remaining debris is meticulously cleared. The cavity may then be irrigated with a scolecidal agent.\textsuperscript{42} The recurrence rate of this procedure is 10% to 30%.\textsuperscript{46}

**Laparoscopic Cyst Evacuation.** Peripherally located echinococcal hepatic cysts may be safely managed by laparoscopic cyst evacuation.\textsuperscript{50} The lesions best suited for this approach are situated anteriorly and do not have thick calcified walls. A right lateral approach also works for cysts in segments VI and VII. A trocar (11 mm) is inserted just above the cyst, and 10% povidone-iodine–soaked sponges are placed as the scolecidal agent. The cyst is aspirated with a 14-gauge needle. The endocyst then shrinks back from the wall and rests at the bottom of the cyst. The 11-mm trocar is then exchanged
for an 18-mm trocar, and the germinal membrane is aspirated. The laparoscopic camera is inserted directly into the cyst to explore for residual daughter cysts or biliary fistulae. The remaining cavity is irrigated with a 20% saline solution, and the cyst wall is excised. The cavity may be plugged with omentum or closed over a closed suction drain.\textsuperscript{50}

The most difficult part of the laparoscopic approach is the initial cyst puncture and aspiration of the cyst fluid. Indications for laparoscopic excision of liver echinococcosis have changed over the years. Currently, the only excluding criteria for laparoscopic intervention are deep intraparenchymal cysts or posteriorly situated cysts, more than 3 cysts, and cysts with thick and calcified walls. Postoperative morbidity ranges from 8% to 25%, and morality in most series is 0% with recurrence rates of 0% to 9% (vs 12%-63% morbidity, 0%-3% mortality, and 0%-30% recurrence in open series). However, major complications (eg, anaphylaxis) are more common in laparoscopic interventions as a result of peritoneal spillage during debridement and removal of cyst contents. Major drawbacks to the comparison of laparoscopic versus open procedures are the small studies, lack of randomization, and bias related to careful selection of laparoscopic candidates.\textsuperscript{46}

**Pericystectomy.** Pericystectomy involves complete resection of the cyst wall without entering the cyst cavity. This procedure is done through a plane outside of the pericyst or along the cyst wall itself. Preoperative localization of the bile ducts and vascular system is imperative. If a bile duct connection is suspected, preoperative ERCP should be obtained. Intraoperative US should be used. Pericystectomy decreases the risk of spillage of cyst contents into the peritoneal cavity and also lowers the risk of recurrence. The disadvantage to this approach is the potential for bleeding and/or damage to bile ducts in proximity to the cyst wall.\textsuperscript{42} Gunay and associates\textsuperscript{38} reported 0% recurrence rates, a lower incidence of biliary fistulae, and shorter hospitalization compared with more conservative procedures. The procedure also precludes management of the cavity and facilitates detection of recurrence.

One of the largest recently published cohorts, including 359 patients, suggested that open pericystectomy should remain the method of choice for complicated liver hydatid cysts. However, a laparoscopic approach may be implemented in simple disease with good results.\textsuperscript{48} In their review of
published literature on laparoscopic management of liver hydatid cysts, Tuxun et al\textsuperscript{51} reported a 0.22\% mortality and 15\% overall complication rate. Most procedures were cystectomies (60\%) of disease types CE1-2 (46\%), whereas more advanced types were also treated by some groups (CE3 14\%, CE4 4\%, CE5 16\%). Conversion rate to open surgery was about 5\%, and recurrence was 1\%, occurring 3 to 68 months after the procedure.\textsuperscript{51}

**Liver Resection/Transplantation.** Some experts have argued that formal resection for benign disease is excessive and unnecessary, whereas others have stressed that resection is very safe. Multiple cysts within proximity to a major blood supply or to each other or cysts in a relatively safe location (ie, segments II and III) are candidates for resection provided a complete resection can be achieved. *E multilocularis* infection also may lead to fulminant hepatic failure from sclerosing cholangitis, biliary sclerosis, or Budd-Chiari syndrome, and in these rare cases, orthotopic liver transplantation may be necessary.\textsuperscript{42} Among these various treatment options, criteria for uncomplicated and complicated patients are presented in Table \textit{56-12}. A recent study also discovered lymphatic spread of larval *E multilocularis* from the liver to regional lymph nodes and suggests the routine removal of regional nodes to reduce the risk of persistent infection.\textsuperscript{52}

\begin{table}
\caption{TREATMENT OPTIONS FOR HYDATID LIVER CYSTS}
\end{table}
**Complications**

Complications from hydatid cysts are seen in one-third of patients. Most commonly, the cyst ruptures internally or externally, followed by secondary infection, anaphylactic shock, and liver failure, in order of decreasing frequency. Viable hydatid cysts are space-occupying lesions with a tendency to grow. In confined areas such as the central nervous system, even small cysts can cause severe symptoms. In less confined areas, symptoms depend on the site and size of the cyst. Symptoms result from direct pressure or distortion of neighboring structures or viscera. Compressive atrophy of the surrounding hepatocytes and fibrosis occurs, and these cysts may grow to such an enormous size that they replace an entire lobe.
As the cysts enlarge, they may also rupture. If rupture of only the endocyst occurs, the content is retained within the pericyst. A communicating rupture is a rupture into the biliary or bronchial tree. Hydatid liver cysts cause compression of the biliary system, leading to decubiti-like lesions and biliary communication in up to 80% of cases. This communication may be very difficult to find and result in biliary leakage/fistulae postoperatively. Bile leakage is the main source of cavity-related complications in conservative surgery. If not properly drained, a bile leak may result in an abscess or bile peritonitis. If drained effectively, an external biliary fistula may develop. Twelve to 33.3% of patients with biliary fistulae require biliary drainage postoperatively, and rates are higher in conservative versus radical surgery. The complication rates for radical surgery range from 17% to 20%. Retention cysts in conservative surgery may lead to misdiagnosis of early recurrence and result in unnecessary operations.

A free rupture occurs when hydatid contents rupture throughout the peritoneal, pleural, or pericardial cavity. Acute symptomatic rupture into the peritoneal cavity occurs in 1% to 4% of patients and may precipitate anaphylactic shock.

**Outcome**

Medical therapy alone results in recurrence rates of 70% to 80% and is not recommended. Medical treatment is used in combination with a drainage procedure or in patients who are not surgical candidates. Uncomplicated cases that undergo open surgical, laparoscopic, or percutaneous drainage have recurrence rates of approximately 10%. Early local recurrence and cavity-related complications are the main problems affecting the success of the surgical management of hydatid liver disease. These problems are rare for complete resections due to complete removal of the cyst wall containing the germinal epithelium and daughter cyst. Conservative operations are easier and safer but are associated with a high incidence of local recurrence (10%) and cavity-related complications (37%). Older cysts have an increased risk of exogenic daughter cyst formation, which is an important risk factor for early local recurrence. Another important risk factor for early local recurrence, especially in conservative surgery, is pre- and intraoperative undetected satellite cysts, which exist around pericysts or exogenic vesiculations. Since
the disease is endemic to many locations, the potential for reinfection remains, so long-term serologic and imaging studies are necessary. Rupture into the pleural or peritoneal cavity portends a recurrence rate of up to 25%. Uncomplicated cases undergoing elective procedures such as laparoscopic or percutaneous cyst aspiration should have morbidity rates between 15% and 30% and essentially no mortality. In patients with complicated disease that requires open evacuation, pericystectomy, or resection, morbidity is as high as 50%; however, mortality should still remain less than 5%. Septic shock, peritoneal rupture, and comorbid conditions (ie, malnutrition) play a major role in increasing mortality rates.

CONGENITAL LIVER CYSTS

Simple

The incidence of simple hepatic cysts in 1695 patients referred for abdominal or pelvic US was 2.5%, with a sharp increase noted at >60 years old. In a separate European study of more than 26,000 patients undergoing upper abdominal US, simple cysts were found in 2.8%, and most patients (>92%) were over the age of 40. The female-to-male ratio was 1.5:1.

Solitary benign cysts are believed to be congenital and thought to arise from abnormal development of intrahepatic bile ducts in utero. The aberrant ducts enlarge slowly and may result in symptoms later in life. In a study from the Mayo Clinic from 1907 to 1971, only 24% of simple cysts were symptomatic, and they usually became symptomatic in the fourth or fifth decade of life. Abdominal pain or a mass was noted most frequently and was present in more than 50% of patients. Less commonly, symptoms were related to mass effect resulting in nausea, vomiting, early satiety, and jaundice. Physical exam revealed hepatomegaly or a palpable abdominal mass. Laboratory values should be normal, but occasionally, hyperbilirubinemia may be seen. Simple solitary cysts are bluish in color and contain clear, straw-colored fluid. Echinococcal disease should be ruled out by serology.

US is the most accurate imaging modality, with greater than 90% sensitivity and specificity. On US, the cysts appear as anechoic masses with
smooth margins and thin, imperceptible walls. US also differentiates between cystic and solid lesions and can assess for intra- and extrahepatic biliary dilatation in the jaundiced patient. CT imaging reveals nonenhancing, fluid (water) density lesions with a thin, uniform wall (Fig. 56-11). On MRI, simple cysts are well-circumscribed lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images.  

**FIGURE 56-11**  CT demonstrating a large simple cyst compressing the hepatic veins and inferior vena cava and abutting the left portal venous system. CT, computed tomography.

Most simple cysts are found incidentally and are asymptomatic, and 80% to 95% remain asymptomatic. In the setting of symptoms, percutaneous aspiration can aid in diagnosis but is associated with 100% recurrence within a 2-year period. If sclerosants are added, a 17% recurrence rate can be achieved.  

Success of surgical treatment for cystic liver disease is judged by relief of
symptoms rather than by complete disappearance of the cystic lesion on imaging studies. Once the benign nature of the cyst is established, a permanent internal cyst “drain” is the mainstay of surgical therapy, and complete cyst excision is not necessary. If the cyst protrudes from the liver and no biliary connection is demonstrated, the accessible wall on the liver surface may be excised and the remaining cyst lining allowed to drain freely into the peritoneal cavity. If the cyst has a biliary connection, suspicion should be high that the lesion is a biliary cystadenoma rather than a simple cyst. In general, cyst excision or unroofing and resection have a 0% to 20% recurrence rate and a mortality rate of 0% to 5% (Table 56-13).

**TABLE 56-13: TREATMENT OPTIONS FOR CONGENITAL LIVER CYSTS**

I. Simple cysts
   A. Aspiration with sclerosis
   B. Open surgery
      1. Partial excision
      2. Complete excision
   C. Laparoscopic surgery
      1. Partial excision
      2. Complete excision
II. Polycystic liver disease
   A. Aspiration with sclerosis
   B. Open surgery
      1. Partial unroofing
      2. Unroofing with resection
      3. Liver transplantation

In recent years, laparoscopy has become the most common approach and has an overall success rate of more than 90% with a 10% rate of symptomatic cyst recurrence. Proponents of the laparoscopic approach report excellent exposure, less postoperative pain, and success rates similar to those of cases done open. The laparoscopic approach has also been associated with a longer time interval to symptom recurrence compared to both open unroofing and resection. Gamblin et al reported the largest series of laparoscopic liver
resections for cystic lesions, which included 51 patients. The authors routinely left the back wall of the cyst behind and untreated. Patients experienced minimal postoperative pain, short hospital stays (median, 2 days; range, 1-11 days), and resolution of symptoms (pain resolved in all) and had a low recurrence rate (2 of 51 patients required reoperation), and there were no 90-day mortalities. Median follow-up was 13 months. A growing body of literature supports the equivalency of many laparoscopic and open procedures with regard to outcomes and advantages in avoiding a laparotomy, especially in benign disease. These authors proposed minimally invasive cyst excision as the standard of care for management of benign hepatic cysts.\(^{59}\)

**Polycystic**

Polycystic liver disease (PCLD) is an autosomal dominant disorder often found in association with polycystic renal disease (40%).\(^{60}\) PCLD is the most frequent extrarenal manifestation of autosomal dominant polycystic kidney disease. PCLD also exists in an autosomal dominant pattern that is not associated with polycystic renal disease, but may have cysts that develop in other organs in addition to the kidneys.

Cysts in PCLD are epithelial-lined growths arising from biliary epithelium that usually do not communicate with the biliary tree. The majority of patients are asymptomatic and do not require treatment. Their prognosis is directly related to the severity of the accompanying renal disease.\(^{61}\)

If PCLD becomes symptomatic, the cause usually is hepatomegaly. Symptoms may include abdominal fullness, distention and pain, or bowel and biliary obstruction. Complications such as bleeding, infection, rupture, portal hypertension, and Budd-Chiari syndrome have been reported but are rare. Malignant transformation also has been reported but occurs infrequently. Hepatic function is typically preserved, so progression to liver failure is uncommon.\(^{61}\)

Routine imaging of cysts in PCLD is similar to that of simple cysts. Unenhanced CTs show multiple, homogenous, hypoattenuating lesions with a regular outline (Fig. 56-12). Contrast-enhanced CT images have no cyst wall or enhancement of cyst contents. MRI demonstrates very low signal intensity on T1-weighted images and does not enhance after administration of gadolinium. Since the cyst content is purely fluid and homogenous, high
signal intensity is demonstrated on T2-weighted images. Based on CT imaging, adult polycystic liver disease can be categorized as follows: type I, limited number (<10) of large cysts with large areas of noncystic parenchyma; type II, diffuse involvement of liver parenchyma by medium-sized cysts with remaining large areas of noncystic parenchyma; and type III, diffuse involvement of liver parenchyma by small- and medium-sized liver cysts with only a few areas of normal liver parenchyma.

FIGURE 56-12 CT demonstrating polycystic liver disease. CT, computed tomography.

Development of symptoms in PCLD is most often due to hepatomegaly; and therefore, treatment needs to result in a reduction of liver size. Percutaneous aspiration with sclerotherapy may be used in patients who are not surgical candidates or in lesions that are not surgically accessible, but long-term results of this approach are poor.

If a small number of large cysts exist, laparoscopic unroofing with the aid of intraoperative US may be successful. Deeper cysts may be accessed and unroofed through the back wall of more superficially located cysts. However,
due to the rigid architecture found in PCLD, unroofing alone may not be enough to provide hepatic collapse and relief of symptoms. In addition, if too many cysts are unroofed, the peritoneum’s absorptive capacity may be exceeded and cause ascites. Unroofing is not useful in patients with a large number of smaller cysts because it cannot be adequately performed.

In PCLD, recurrence of symptoms is common and has been reported in up to 57% of patients after open and 72% after laparoscopic approaches. In a comparative study between open unroofing, laparoscopic unroofing, and resection in patients with liver cysts, in the polycystic liver disease subset, laparoscopic unroofing was associated with the highest recurrence of symptoms (85%). However, symptoms were less severe. Time to symptom recurrence was longer compared to open unroofing and comparable to resection. No difference was identified in quality of life by type of surgical approach. However, the quality of life in patients with recurrence of symptoms was better after laparoscopic unroofing compared to resection.

A combination of cyst unroofing and liver resection may achieve the best results in terms of reducing liver volume. Resection should include the most cysts with the least loss of hepatic function. Morbidity for this approach is greater, but long-term results are improved. Orthotopic liver transplant is occasionally indicated if symptoms are disabling or hepatic function is compromised. If patients have associated renal failure, the liver transplant may be combined with renal transplantation.61

**NEOPLASTIC CYSTS**

Neoplastic cysts are acquired cysts that occur less commonly than simple cysts, usually in females, in the fifth decade of life. Their etiology is unknown. Cystic neoplasms are frequently large, resulting in abdominal discomfort and a palpable mass on examination. Cystic neoplasms appear as multiloculated lesions with papillary projections inside the cyst cavity. Invasion of the surrounding tissue suggests malignancy, as does the presence of a predominantly solid (vs cystic) component. Ten percent of neoplastic cysts are malignant. Definitive diagnosis requires intraoperative biopsy of the cyst wall. Incomplete resection will result in nearly 100% recurrence.57

Laboratory investigation is normal in most, although some patients present with elevated liver enzymes. Serum α-fetoprotein (AFP) and
carcinoembryonic antigen (CEA) levels are usually normal. In some patients, CA 19-9 has been found to be elevated five fold. In general, hemorrhagic cyst fluid suggests cystadenocarcinoma, whereas bilious or mucinous fluid suggests cystadenoma.\textsuperscript{62}

**Cystadenoma**

Cystadenomas comprise less than 5% of all intrahepatic cysts of biliary origin.\textsuperscript{63} Hepatobiliary cystadenoma with mesenchymal stroma occurs exclusively in young- and middle-aged women and has potential to transform into cystadenocarcinoma. In contrast, hepatobiliary cystadenoma without mesenchymal stroma occurs in both sexes equally, at a mean age of 50 years, and has no clear association with cystadenocarcinoma.\textsuperscript{62} These tumors are lined with columnar epithelium and frequently have papillary infoldings.\textsuperscript{63} If symptoms are present, they may include abdominal pain (60%-80%), jaundice, cholangitis, fullness, or bloating.\textsuperscript{1}

Cystadenomas have a septated, multilocular appearance on US and CT (Fig. 56-13).\textsuperscript{57} CT will reveal well-demarcated cystic lesions, usually with internal septations; the walls are rarely calcified, and the presence of polypoid protrusions or wall excrescences should trigger the concern for cystadenocarcinoma.\textsuperscript{1} MRI shows typical features for a fluid-containing loculated mass with homogeneous low signal intensity on T1-weighted images and homogeneous high signal intensity on T2-weighted images. However, signal intensity of mucinous fluids vary depending on protein concentration. On T1-weighted images, the signal intensity may change from hypointense to hyperintense as protein concentration increases. On T2-weighted images, signal intensity of mucinous fluids can decrease from hyperintense to highly hypointense with increasing protein concentration and viscosity. Blood products also have different signal characteristics on MRI. The distinction between cystadenoma and cystadenocarcinoma remains difficult based on imaging findings alone, as the presence or absence of septae, mural nodules, and papillary projections is variable between lesions. MRCP does, however, appear helpful in evaluating the relationship of the lesion to the bile ducts.\textsuperscript{64} ERCP will usually demonstrate communication with the biliary tree, often at the proximal left hepatic duct.
FIGURE 56-13  A. Ultrasound demonstrating a septated cystic liver tumor.  B. Intraoperative photograph of segment IV liver cystadenoma.  C. Gross photograph of liver cystadenoma after enucleation.

Serum CEA and CA 19-9 levels are usually within normal ranges and cannot be considered as significant parameters to discriminate between malignant and benign liver tumors.\(^6^4\) The diagnosis of intrahepatic biliary cystadenoma can be suggested on the basis of cyst fluid analysis (CFA), but this relies on adequate sampling and correlation with clinical and radiologic findings. CA 19-9 and CEA have been shown to be elevated in intrahepatic biliary cystadenoma and normal in simple cysts. Immunohistochemical analysis of intrahepatic biliary cystadenoma has shown the presence of CA 19-9 and CEA in the epithelium; however, the premalignant progression is based on the histologic presence of intestinal metaplasia characterized by the presence of numerous goblet cells. This observation has led to the recommendation that patients with suspected intrahepatic biliary cystadenoma based on CFA should undergo cyst wall sampling to determine whether a premalignant (intestinal metaplasia plus atypia) or malignant diagnosis requiring resection exists.\(^6^5\) Other authors, however, believe that percutaneous biopsy for preoperative diagnosis rarely produces a definitive diagnosis and the risk of peritoneal dissemination in the case of malignancy is prohibitive.

Neoplastic cysts with no signs of malignancy may be enucleated. This technique requires removal of the entire cyst, the cyst’s surrounding wall, and a small rim of liver parenchyma.\(^5^7\) Formal hepatic resection also is an appropriate treatment. Aspiration, sclerosis, marsupialization, and internal drainage must be avoided. Inadequate excision leads to recurrence in all cases\(^6^3\) (Table 56-14).

| TABLE 56-14: TREATMENT OPTIONS FOR NEOPLASTIC LIVER CYSTS |
I. Cystadenoma
   A. Enucleation
   B. Hepatic resection
II. Cystadenocarcinoma
   A. Hepatic resection
   B. Palliative unroofing

**Cystadenocarcinoma**

Devaney and colleagues\textsuperscript{66} divided cystadenocarcinoma (Fig. 56-14) into 3 subtypes: (1) cystadenocarcinoma with mesenchymal stroma arising from cystadenoma with mesenchymal stroma, occurring exclusively in females and following a relatively indolent course; (2) cystadenocarcinoma without mesenchymal stroma not associated with cystadenoma, occurring in males and following an extremely aggressive course; and (3) cystadenocarcinoma without mesenchymal stroma, occurring in females and with a poorly understood clinical course.\textsuperscript{67} Resection is the only appropriate treatment for malignant biliary cystadenocarcinoma.\textsuperscript{57} With complete resection, the clinical course for cystadenocarcinoma is better than that for hepatocellular carcinoma or cholangiocarcinoma,\textsuperscript{67} with a reported 65% to 70% 5-year survival after complete resection.
On the contrary, partial excision predisposes to local recurrence and a significantly worse 5-year survival of 36%. Extrahepatic recurrence is rare but may be observed in up to 20% of patients. A recently published multicenter retrospective cohort review reported an overall survival of 8.4 years.68 Worse survival was associated with the presence of spindle cell/ovarian stroma. The available evidence on the role of other treatment modalities, such as chemotherapy and radiation, is limited to few single-center reports. Definitive chemotherapy and radiation for unresectable disease has previously been reported to confer a 33% 5-year survival. In the rare patient with a symptomatic cystadenocarcinoma with peritoneal metastases, palliative unroofing of the cyst may be indicated.

TRAUMATIC CYSTS

In recent years, the management of hepatic trauma has undergone major changes. The frequent use of dual-phase CT imaging to assess patients with
abdominal trauma has resulted in the detection of even the most minor of liver injuries. In the hemodynamically unstable patient, damage control laparotomy—the control of bleeding and contamination with packing off of the abdomen to postpone definitive treatment—has gained popularity, while formal anatomic hepatic resection has fallen out of favor. More American Association for the Surgery of Trauma grade IV and V liver injuries also are being managed nonoperatively. Mortality rates have fallen to 7% to 12%, but a different set of management problems is being created. One such problem is the traumatic liver cyst.

Traumatic hepatic cysts are acquired cysts that occur from continued bile leakage from an injured intrahepatic bile duct after abdominal trauma. When an injured biliary structure continues to leak into a hematoma cavity, a cyst containing bile and blood may form. These cysts lack a true epithelial lining and are considered pseudocysts (Fig. 56-15). Some traumatic cysts may resolve spontaneously, while others may grow until compressive symptoms develop. Presentation is typically delayed, and abdominal pain or fullness may occur months or sometimes years after the trauma.
FIGURE 56-15  A. CT scan demonstrating a traumatic hepatic cyst 4 months after blunt liver trauma. B. Ultrasound in the same patient demonstrating a thickened cyst wall. CT, computed tomography.
Treatment

Treatment is reserved for patients who are symptomatic. Options include aspiration, unroofing, and excision. Bile leaks must be sought and controlled. Small bilomas may be observed, whereas larger collections usually require percutaneous drainage at the time of diagnosis. Once the cavity is collapsed, spontaneous closure of the fistula is the rule.

REFERENCES

17. Lederman ER, Crum NF. Pyogenic liver abscess with a focus on Klebsiella pneumoniae as a primary pathogen: an emerging disease with unique clinical characteristics. Am J Gastroenterol.


Benign liver neoplasms encompass a variety of liver lesions, each with distinct pathologic, radiographic, and molecular characteristics. These include hemangioma, focal nodular hyperplasia, hepatocellular adenoma, and other less commonly seen lesions (Table 57-1). Benign liver lesions occur in up to 20% of the population and far surpass the incidence of malignant liver lesions. With the increased utilization of cross-sectional imaging, these tumors are being identified more frequently. Benign liver lesions are usually asymptomatic and are generally observed. Surgical intervention is warranted in symptomatic patients, cases where malignancy cannot be excluded, or if there is a potential for malignant transformation or associated complications (Fig. 57-1). Liver lesions with equivocal imaging characteristics can lead to diagnostic uncertainty resulting in important therapeutic ramifications. As a result, a thorough understanding of benign liver neoplasms is necessary to more accurately and appropriately screen patients for expectant management versus surgical intervention.
Solitary solid liver lesion on US or CT

MRI/multiphasic CT

Hepatic adenoma

< 5 cm, Asymptomatic

Observation

> 5 cm, Symptomatic

Resection

Focal nodular hyperplasia

Asymptomatic

Symptomatic

Hepatic hemangioma

Unknown

Core needle biopsy

Unknown

FIGURE 57-1 Treatment algorithm for solitary liver lesions. CT, computed tomography; MRI, magnetic resonance imaging.
HEMANGIOMA

Epidemiology and Etiology

Hepatic hemangiomas are the most common benign tumor of the liver, affecting up to 20% of the population.\(^1,2\) Hemangiomas occur predominantly in females (60%-80%) and typically present in the third to fifth decades of life.\(^3-5\) Hemangiomas may be isolated to the liver or associated with systemic syndromes.\(^6\) In nearly 50% of patients, hepatic hemangiomas are multifocal.\(^7\)

The etiology of hepatic hemangiomas is poorly defined. They are thought to arise either as congenital lesions that enlarge due to vascular ectasia or as vascular enlargement from previously normal hepatic vasculature. The blood supply of hepatic hemangiomas is derived from the hepatic artery. Commonly seen characteristics suggest a role of estrogens in their pathogenesis. These include female predominance, increase in size during pregnancy, and change in size while taking oral contraceptive pills (OCPs), as well as association of estrogen replacement therapy with hemangioma recurrence.\(^8-10\) The association of hormones and hemangioma does, however, remains controversial. For example, a case-control study showed no association between liver hemangioma and a history of OCP use.\(^11\) However, Glinkova et al. performed a prospective evaluation of 94 women with 181 hemangiomas and concluded that hormone therapy increased the risk of hemangioma enlargement.\(^7\) Although the association of hormone therapy and hepatic hemangioma pathogenesis remains poorly understood, hepatic hemangioma patients with nonphysiologic exposure to sex hormones warrant serial close observation.

Pathology

Grossly, cavernous hemangiomas are soft, compressible, blood filled, and well-defined tumors. Hemangiomas can be multifocal and of variable size. Hemangiomas greater than 5 cm in size are typically considered “giant” hemangiomas. Microscopically, hemangiomas consist of a single layer of benign endothelium along vascular channels separated by thin connective tissue. Cystic degeneration, thrombosis, fibrosis, and calcifications may be
present. Estrogen and progesterone receptors are not typically seen.\textsuperscript{12}

Hepatic hemangiomas are generally not encapsulated and the liver parenchyma–hemangioma interface varies (Fig. 57-2). Zimmerman and Baer described this variation and its clinical implications.\textsuperscript{13} Most commonly, the liver parenchyma–hemangioma interface consists of capsule-like, avascular fibrous lamellae, making hemangiomas more amenable to enucleation. The second pattern, known as the interdigitating interface, has components of the hemangioma projecting into the associated liver parenchyma without fibrous lamellae. A third pattern is characteristic of highly irregular borders without clear delineation of liver parenchyma versus the hemangioma. The fourth and final interface lacks fibrous tissue between the hemangioma and liver parenchyma. In this case, the hemangioma is in direct contact with the liver parenchyma leading to a smooth, regular interface that includes dilated portal vein branches and microhemangiomas. The lack of a fibrous capsule in the latter three patterns complicates attempts at enucleation.

\textbf{FIGURE 57-2} High magnification microscopic appearance of hepatic hemangioma with multiple blood-filled vascular channels lined by a single layer of flat epithelium. (Used with permission from Dr. Robert Anders, MD, PhD.)
Clinical Presentation and Diagnosis

Hepatic hemangiomas are typically asymptomatic and found incidentally during imaging studies obtained for other reasons. Symptomatic hemangiomas occur in 10% to 50% of cases. Not unexpectedly, larger lesions are more likely to produce symptoms.\(^3,14\) Associated symptoms include right upper quadrant pain, general abdominal pain, nausea, and early satiety as a result of compression of adjacent structures. Potential life-threatening complications may include hemorrhage, hemobilia, rupture, and hemangioma-associated heart failure; however, each of these complications is very uncommon. In fact, less than 5% of hemangiomas will present after spontaneous rupture. However, if a patient does present with rupture, disseminated intravascular coagulation, hemodynamic instability, and hypovolemic shock are seen in up to one-third of these cases.\(^4,15\) Spontaneous rupture of a liver hemangioma has an estimated mortality of approximately 35%.\(^16\) Kasabach–Merritt syndrome is a life-threatening complication often triggered by a dental or surgical procedure in patients with giant hemangiomas. It consists of thrombocytopenia and disseminated intravascular coagulopathy, and patients present with acute right upper quadrant pain and bleeding.

Diagnosis of a hepatic hemangioma is typically accomplished via imaging (Table 57-2). On ultrasound, hemangiomas appear as a well-defined, hyperechoic mass (Fig. 57-3A). The echogenicity can vary secondary to internal fibrosis, thrombosis, and necrosis.\(^2\) Unenhanced abdominal computed tomography (CT) depicts a hypodense or isodense lesion within the liver parenchyma, and an unenhanced scan can often miss hemangioma lesions. Multiphasic CT and magnetic resonance imaging (MRI) are highly sensitive and are most useful in differentiating hemangiomas from other hepatic lesions. Early peripheral enhancement that proceeds toward central enhancement is generally diagnostic. MRI has a better sensitivity (91%) and specificity (92%) than CT\(^2\) (Fig. 57-3B-F). MRIs with heavily weighted T2 imaging typically show delayed relaxation times and can reliably differentiate hemangioma from metastatic disease with an accuracy of 97%.\(^17\) Positron emission tomography scans may be helpful in differentiating hemangiomas from metastatic disease given that hemangiomas are not \(^18\)F-fluorodeoxyglucose (FDG)-avid—although this is rarely necessary.
Technetium-99m-labeled red blood cell scans can also be used in instances where CT and MRI are nondiagnostic, although this test is also seldom needed.

**TABLE 57-2: IMAGING CHARACTERISTICS OF HEPATIC HEMANGIOMA, FOCAL NODULAR HYPERPLASIA, AND HEPATIC ADENOMA**

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>CT</th>
<th>MRI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic hemangioma</td>
<td>Well-defined, hyperechoic</td>
<td>Hypoattenuating on noncontrast CT</td>
<td>T1: hypointense, T2: hyperintense with respect to the liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arterial phase shows peripheral, discontinuous enhancement</td>
<td>T1 + Gadolinium; peripheral, discontinuous nodular enhancement with centripetal filling on delayed images</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portal venous phase shows centripetal filling and hyperattenuating lesion</td>
<td>T1 + Evist: variable appearance</td>
</tr>
<tr>
<td>FNH</td>
<td>Variable echogenicity and difficult to visualize</td>
<td>Hypo or isoattenuating lesion with hypoattenuating central scar on noncontrast CT</td>
<td>T1: isointense with hypointense central scar T2: isointense with hyperintense central scar T1 + Gadolinium: intense arterial phase, isointense to liver on portal venous phase T1 + Evist: early arterial enhancement, persists in delayed phases, remaining slightly enhanced on hepatobiliary phase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arterial phase shows hyperattenuating lesion with hypoattenuated central scar</td>
<td>Technetium 99m sulfur colloid scan positive (80% of cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhanced on delayed phases in 80% of cases</td>
<td></td>
</tr>
<tr>
<td>Hepatic adenoma</td>
<td>Well-defined, typically solitary lesion with variable echogenicity depending on fat and blood content</td>
<td>Well demarcated with variable attenuation depending on blood (hyperattenuating) and fat (hypoattenuating) content</td>
<td>T1+ Gadolinium: early arterial enhancement followed by rapid isointensity to liver on delayed images T1 + Evist: hypointense on hepatobiliary phase</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; FNH, focal nodular hyperplasia; MRI, magnetic resonance imaging.
Invasive diagnostic procedures are unnecessary and are typically contraindicated given the high likelihood of complications. Liver function tests are generally normal except in cases of obstructive jaundice secondary to parenchymal compression or in cases of Kasabach-Merritt syndrome. Biopsy of hepatic hemangioma is highly unreliable and is associated with a high risk of bleeding, and therefore is contraindicated when hepatic hemangioma is suspected.3

**Treatment**

Hepatic hemangiomas typically remain stable in size, and radiographic changes are unlikely.18 As a result, observation is warranted in both
asymptomatic and minimally symptomatic patients.\textsuperscript{3} Gestational hepatic hemangiomas behave similarly to lesions in nonpregnant patients. Accordingly, asymptomatic lesions may be followed in both pregnant patients and patients taking hormone replacement therapy.

Indications for surgical resection include severely symptomatic lesions, patients with hemangioma-related complications (ie, rupture or Kasabach–Merritt syndrome), and patients with indeterminate liver lesions where malignancy cannot be ruled out. Of note, size is not a criterion for operative intervention. In a retrospective series of 492 patients with giant hemangiomas, long-term outcomes were available in 289 survey responders. Clinical observation resulted in a similar incidence of hemangioma-related complications/symptoms versus operatively managed patients\textsuperscript{19} (Table 57-3).

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**TABLE 57-3: COMPARISON OF ADVERSE OUTCOMES DURING FOLLOW-UP BETWEEN NONOPERATIVELY AND OPERATIVELY MANAGED HEPATIC HEMANGIOMAS**

<table>
<thead>
<tr>
<th>Type of Adverse Event\textsuperscript{a}</th>
<th>Nonoperative Group (n = 233)</th>
<th>Operative Group (n = 56)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative morbidity</td>
<td>8</td>
<td>14</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Persistence of symptoms or complications</td>
<td>144 (21)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>New onset of symptoms or complications</td>
<td>20</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Need for intervention or reoperation</td>
<td>14</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Total patients with adverse events</td>
<td>144 (21)</td>
<td>14 (20)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

\textsuperscript{a} More than one type of adverse outcome per patient possible.


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**TABLE 57-4: HEPATIC ADENOMA SUBTYPE AND RADIOGRAPHIC FEATURES**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percent</th>
<th>Genetic Alteration</th>
<th>Gadolinium-Enhanced T1 Weighted-MRI Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta)-catenin-mutated HA</td>
<td>10-15</td>
<td>(\beta)-catenin</td>
<td>No specific MR imaging patterns; strong arterial phase enhancement and portal venous washout</td>
</tr>
<tr>
<td>HNF1-(\alpha) -mutated HA</td>
<td>30-45</td>
<td>HNF1-(\alpha)</td>
<td>Moderate enhancement in the arterial phase, no persistent enhancement on portal venous or delayed phase</td>
</tr>
<tr>
<td>Inflammatory HA</td>
<td>40-55</td>
<td>IL6ST (65%), STAT3 (6%), GNAS (5%), Unknown (24%)</td>
<td>Intense enhancement during arterial phase persisting in the portal venous and delayed phase</td>
</tr>
<tr>
<td>Unclassified</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Operative approaches for hepatic hemangiomas include enucleation and formal anatomic or nonanatomic liver resection. Hemangioma enucleation is associated with reduced loss of functional hepatic parenchyma, less perioperative blood loss, and fewer complications compared with formal liver resection.\textsuperscript{3,20} As a result, enucleation is the most commonly employed surgical technique. Peripheral lesions are particularly amenable to this approach. Enucleation typically begins with control of hepatic artery inflow via a Pringle maneuver. The ipsilateral hepatic artery is identified. For larger lesions, ligation of the ipsilateral hepatic artery may be necessary, whereas in smaller hemangiomas, hepatic artery inflow can be controlled with ligation of more distal branches. Division of hepatic parenchyma is then performed via gross identification of the hemangioma to normal parenchyma border. Control of bile ducts and small blood vessels is obtained while transecting through the compressed sheath of liver tissue representing the hemangioma–normal liver parenchyma interface.

**Prognosis**

Follow-up imaging as suggested by Mezhir et al. is recommended.\textsuperscript{21} This consists of follow-up MRI 3 months after diagnosis along with a repeat MRI in 3 to 6 months for atypical lesions with low suspicion for malignancy. More infrequent follow-up is appropriate once the diagnosis and stability of the lesion have been documented. Recurrence is rare after definitive treatment. These instances are commonly associated with estrogen therapy.\textsuperscript{9} As noted above, hemangiomas in pregnant patients or patients receiving exogenous estrogen may have a higher likelihood to increase in size.\textsuperscript{7} As a result, these patients warrant careful observation.\textsuperscript{7,22}

**FOCAL NODULAR HYPERPLASIA**

**Epidemiology and Etiology**

Focal nodular hyperplasia (FNH) is the second most common benign solid liver tumor. Its prevalence is estimated to be between 0.3\% to 3\% based on autopsy analysis.\textsuperscript{23} FNH occurs predominantly in females (8:1 female-to-
male ratio). The average age of presentation is 35 years old. FNH tumors are composed of a cluster of benign-appearing hepatocytes within the background of normal-appearing hepatic parenchyma.\textsuperscript{24}

FNH is thought to arise from a vascular malformation or a vascular injury and subsequent expansion of proliferative hepatocytes.\textsuperscript{25} Its association with vascular abnormalities is further supported by studies demonstrating a higher prevalence of FNH in families with hereditary hemorrhage telangiectasia.\textsuperscript{26} Furthermore, in a series of 148 patients with FNH, 20\% of patients had concomitant hepatic hemangiomas.\textsuperscript{27} An association with dysregulation of angiopoietin genes ANGPT1 and ANGPT2 has also been suggested.\textsuperscript{28}

FNH and its association with oral contraceptives remains controversial. Approximately 50\% to 75\% of patients with FNH report a history of oral contraceptive use. Moreover, estrogen receptor expression within FNH specimens has been reported.\textsuperscript{29,30} However, other studies indicate that there is no direct association between FNH and oral contraceptives or sex hormones.\textsuperscript{31-33} For example, in their analysis of 216 patients, Mathieu and colleagues concluded that neither the size nor the number of FNH lesions was influenced by OCP use.\textsuperscript{31} Size changes during follow-up were rare and were not associated with OCP use.

**Pathology**

FNH lesions are benign lesions without malignant potential. They grossly appear as brown or tan nodules composed of proliferative, polyclonal hepatocytes and lack the presence of a true capsule\textsuperscript{24} (Fig. 57-4A). Approximately 80\% of patients present with solitary lesions that are variable in size (1 mm-20 cm).\textsuperscript{25,34} A central scar (80\%) and bile duct proliferation (100\%) are characteristics of FNH lesions\textsuperscript{34} (Fig. 57-4B,C).
Focal nodular hyperplasia falls into one of two categories: typical or atypical. Typical or classic FNHs comprise 80% of all FNH cases and contain all of the classic features: lesion with normal appearing hepatocytes, proliferative bile ducts, and a central scar containing abnormal arteries but limited portal veins. Atypical FNH lacks at least one of these classic features. Atypical FNH lesions are further classified into three categories: telangiectatic, FNH with cytological atypia, and mixed hyperplastic or adenomatous FNH. More recently, telangiectatic FNH has been reclassified as a hepatic adenoma subtype as a result of molecular analysis; surgical resection is warranted in the case of telangiectatic FNH/hepatic adenoma.

Microscopically, nodular hyperplastic parenchyma is characteristic. Although hepatocytes are normal in appearance, the surrounding hepatic parenchyma is distorted and portal triads are sometimes lacking. Unlike hepatic adenoma, Kupffer cells and sinusoids are also present. Overall, FNH appears as a hyperplastic process containing components of normal liver but in a disorganized fashion.

Clinical Presentation and Diagnosis

FNH is typically discovered incidentally in young females of reproductive age. Approximately 80% of FNH lesions are asymptomatic, and abnormal liver functions tests are rare (12%-13%). Definitive diagnosis is essential to avoid unwarranted interventions, and this can typically be accomplished through multimodality imaging. On ultrasound, FNH is isoechoic to the liver and can be difficult to identify. Noncontrast CT shows an isointense lesion within the liver background. Contrast-enhanced imaging is generally diagnostic. FNH enhances on arterial phase CT, but unlike hemangioma, there is no centripetal progression. Moreover, the central scar is visualized as hypointense with respect to the rest of the lesion and the normal liver.
Dedicated liver protocol MRI is highly sensitive (70%) and specific (98%) for FNH. FNH is iso/hypointense to normal liver on T1 weighted imaging, including the central scar (Fig. 57-5). These lesions are iso/hypointense on T2 weighted imaging; however, the central scar in this case will be hyperintense. The addition of gadolinium contrast to MRI produces a similar pattern to contrast-enhanced CT, where there is a global, rapid enhancement of the lesion with respect to the rest of the liver. The introduction of gadolinium-based hepatobiliary-excreted contrast agents such as Eovist and Gd-EOB-DTPA has significantly improved the ability to radiographically diagnose FNH. These are particularly helpful in differentiating FNH from hepatic adenoma given that adenomas will not have any contrast uptake on delayed phases. In a recent systematic review and meta-analysis, high/isointensity signal intensity on hepatobiliary imaging was highly accurate in distinguishing FNH from hepatic adenomas with a reported sensitivity of 93.9% and specificity of 95.3% (Fig. 57-5E).
FIGURE 57-5  Focal nodular hyperplasia in a 48-year-old male. Axial unenhanced T1-weighted (A) and T2-weighted (B) images show subtle isointense lesion (arrow) in the right lobe. T1-weighted image in the hepatic arterial phase shows homogeneous enhancement of the mass (C) which becomes isointense to the liver parenchyma in the portal venous phase (D). (E) Delayed (10-minute) phase of enhancement using a hepatobiliary contrast agent demonstrates increased uptake within the lesion (arrow). These findings are consistent with focal nodular hyperplasia. (Used with permission from Ihab Kamel MD and Sepideh Besharati MD.)

Technetium-99m sulfur colloid scintigraphy depicts Kupffer cell activity and therefore can be used in cases of suspected FNH. Eighty percent of these lesions demonstrate uptake of the sulfur colloid. This scan can be helpful in distinguishing FNH from other liver lesions such as hepatic adenomas,
hepatocellular carcinoma (HCC), and hepatic metastases, which typically contain minimal to no Kupffer cells. The sensitivity and specificity of MRI, however, has led to a dramatic decrease in the need for technetium-99m scans.

In cases of imaging discrepancy or uncertainty, biopsy prior to definitive therapy is appropriate. Biopsy should be done, however, only after appropriate imaging modalities have been performed, particularly MRI with gadolinium-based hepatobiliary-excreted lesions, which reduce unnecessary interventions.37

**Treatment**

FNH is benign and not premalignant. The natural history of these lesions is one of limited to no growth, and FNH lesions rarely cause symptoms. Therefore, operative intervention for FNH is seldom required. The standard therapy of FNH is observation. For patients taking OCPs, cessation of OCPs remains a warranted recommendation.29,38 Surgical resection is indicated when there is an inability to rule out malignancy or in the rare instances of rapid growth (particularly with increasing symptoms).39-41 When necessary, surgery generally involves enucleation, as it is associated with fewer complications than a formal liver resection and preserves normal hepatic parenchyma. Liver resection is appropriate when enucleation is unsafe or in instances where malignancy cannot be excluded. The authors prefer nonanatomic liver resections for FNH given the indolent nature of these lesions and the desire to preserve as much normal hepatic parenchyma as possible. In addition, minimally invasive approaches deserve consideration.42

**Prognosis and Follow-Up**

As noted above, FNH rarely causes symptoms and the likelihood of complications is low. As a result, serial observation is safe and is warranted for most cases.21 There are a lack of data describing the appropriate timeline for follow-up. We have adopted the approach described by Mezhir et al. that consists of follow-up MRI 3 months after diagnosis along with a repeat MRI in 3 to 6 months for atypical lesions with low suspicion of malignancy.21
HEPATOCELLULAR ADENOMA

Epidemiology and Etiology

Similar to FNH, hepatic adenomas occur predominantly in young females, with a female-to-male ratio of 11:1. \(^1\) Although their etiology is poorly understood, the association with oral contraceptives is well established. The overall incidence of hepatic adenomas is approximately 1/1,000,000 in the general population; however, the incidence can range from 0.1 to 4 per 100,000 among users of OCPs. \(^1,43\) The duration of OCP use directly correlates with the risk of developing hepatic adenomas. Moreover, OCP users are more likely to present with larger tumors and incur adenoma-associated complications. \(^44\)

In addition to OCPs, hepatic adenomas are associated with androgenic steroid use, glycogen storage diseases, familial diabetes mellitus, and galactosemia. \(^45,46\) Recent data have noted the higher incidence of multifocal adenoma disease, adenomas in men, and non-OCP associated adenomas in females. \(^47\) Furthermore, the increased utilization of cross-sectional imaging has led to a higher incidence of incidentally discovered hepatic adenomas. \(^47\)

Malignant transformation is rare and adenomas often regress with discontinuation of the stimulus (ie, OCPs). The understanding of hepatic adenoma etiology and its malignant risk has been strengthened by the pathomolecular classification of these lesions introduced in 2006. Based on this classification, hepatic adenomas are broken down into four subtypes: hepatocyte nuclear factor-1-α (HNF1-α), β-catenin-mutated hepatic adenomas, inflammatory (telangiectatic), and unclassified. \(^48-50\) This classification separates these lesions into subtypes with specific imaging characteristics, natural history, and clinical behavior such as higher malignant potential (ie, β-catenin-mutated subtype).

Pathology

Hepatic adenomas are well-circumscribed tumors of epithelial origin. Although they lack a true capsule, adenomas are soft, light-colored lesions with identifiable borders against the normal parenchyma (Fig. 57-6A).
Hepatic adenomas are generally solitary (75%), although multiple adenomas are commonly seen with glycogen storage disease or hepatic adenomatosis. Hepatic adenomatosis is defined as multiple adenomas, typically greater than 10 adenomas, and is associated with a germline mutation of HNF1-α. Adenomas can range in size from 1 to 20 cm. Patients with OCP-related adenomas typically have a single large adenoma, while those with glycogen storage disease have numerous, small, poorly circumscribed adenomas dispersed throughout the liver.

**FIGURE 57-6** (A) Gross sectioned pathological specimen of a resected hepatic adenoma represented as single tan globular mass which bulges from the cut surface and is well demarcated from the surrounding liver. (B) Light microscopy view of hepatic adenoma with cords of uniform hepatocytes without an acinar architecture. (Used with permission from Dr. Robert Anders, MD, PhD.)

Microscopically, hepatic adenomas appear similar to normal liver parenchyma. Hepatic adenomas consist of benign-appearing hepatocytes organized into sheets or cords (Fig. 57-6B). Characteristic features that can facilitate differentiation from normal parenchyma include an absence of portal tracts, minimal central veins, and hepatocytes with large amounts of glycogen and lipid. In addition, the absence of bile ducts in adenomas differentiates these lesions from FNH. Given the prognostic implications of the β-catenin-mutated subtype, glutamine synthase staining is now recommended.
Clinical Presentation and Diagnosis

The majority of hepatic adenoma patients present after an incidental finding on imaging or for other reasons such as nonspecific abdominal discomfort. Hepatic adenoma is generally a solitary lesion in the setting of normal liver function tests and no elevation in α-fetoprotein levels. Symptomatic adenomas can be due to large lesions that stretch the capsule of the liver or present in the setting of rupture with acute abdominal pain or hemodynamic instability. In cases of hepatic adenomatosis, approximately 40% of patients

![Figure 57-7](image-url)  
present with acute abdominal pain, and the bleeding rate is nearly 50%. The risk of hepatic adenoma rupture is associated with lesion size greater than 5 to 7 cm and is typically higher among patients taking OCPs. Risk factors for bleeding include exophytic growth, adenomas greater than 4 to 5 cm in size, peripheral liver location, and visualization of lesion-associated arteries.

Approximately 5% to 10% of all hepatic adenomas will progress to hepatocellular cancer. Risk factors associated with malignant risk include male sex, steroid use, size greater than 5 cm, glycogen storage disease, history of steroid intake, and hepatic adenoma molecular classification (Fig. 57-7). β-catenin-mutated adenomas have the highest risk of developing into HCC. Inflammatory hepatic adenomas have only a 10% malignancy risk, while HNF1-α subtypes have a negligible risk. The association of adenoma subtype and bleeding risk remains controversial. Despite earlier studies reporting a higher risk of bleeding in inflammatory subtypes, a recent systematic review by Van Aalten et al. found no difference in the bleeding or rupture risk among the adenoma subgroups.

Adenomas are commonly first identified via ultrasound for right upper quadrant pain. The lesion typically appears as hyperechoic given the high lipid content. Intratumoral hemorrhage results in increased echogenicity, and Doppler view can demonstrate active hemorrhage or intralesional vessels. On noncontrast CT, hepatic adenomas are isoattenuating. Increased fat content or intratumoral hemorrhage leads to hypo- or hyperattenuation, respectively. Contrast-enhanced CT demonstrates a well-demarcated lesion on the arterial phase. This enhancement is short-lived and serves to differentiate these lesions from FNH, which typically have delayed washout.

The best imaging modality to diagnose hepatic adenomas is MRI (Fig. 57-8). In general, adenomas may be hyper- or hypoattenuated depending on the blood and/or fat content, respectively. Gadolinium-enhanced MRI demonstrates arterial enhancement with immediate washout and isointensity of the liver on the portal phase. Although their appearance can be variable and nonspecific, some adenoma subtypes have specific MRI characteristics. Inflammatory hepatic adenoma lesions are diffusely hyperintense on T2 images while gadolinium-enhanced T1 images show intense enhancement in the arterial phase and persistent enhancement in the delayed phase. HNF1-α-mutated hepatic adenoma, on the other hand, lack the persistent enhancement.
on the delayed phase. β-catenin-mutated hepatic adenoma does not have a specific MRI pattern.

**FIGURE 57-8** Hepatocellular adenoma in a 43-year-old female with history of adenomatosis. Axial T-1 weighted-in phase image of the liver (A) shows a mass that is slightly hyperintense (arrow) with significant signal loss on the out of phase image (B). These findings are consistent with a lipid-containing lesion. T1-weighted MR image in the hepatic arterial phase (C) shows a hypervascular mass that washes out in the portal venous phase (D). These
findings are suspicious for hepatocellular adenoma in this patient with pathologically proven adenomatosis. (Used with permission from Ihab Kamel MD and Sepideh Besharati MD.)

In cases of uncertainty after diagnostic imaging, biopsy is warranted. Both fine needle aspiration and core needle biopsy are appropriate. Core needle biopsy remains, however, the gold standard for the diagnosis of hepatic adenoma subtype. The combination of MRI and biopsy is highly reliable in identifying adenoma subtype.

Treatment

The propensity for malignant transformation and hemorrhage make many hepatic adenomas a surgical disease. Surgical resection is offered to patients with symptoms, as well as those patients deemed to be at risk for bleeding or malignant transformation. These risk factors include lesions greater than 5 cm in size, history of bleeding, imaging characteristics concerning for hepatocellular cancer, and β-catenin-mutated subtype. The number of lesions does not dictate therapeutic interventions. Surgical resection consists of complete resection with negative margins. Wide resection margins and lymphadenectomy are not indicated. Acceptable approaches include enucleation, nonanatomic liver resection, and formal liver resection. When feasible, a laparoscopic approach is safe and appropriate. In patients presenting with acute hemorrhage, aggressive resuscitation and interventional radiology-guided selective hepatic artery embolization is the standard of care as initial therapy. Elective surgical resection should then be offered once the patient is stabilized and the hematoma has regressed, which is generally 6 weeks later. Radiofrequency ablation is indicated in unresectable patients with centrally located adenomas or those with severe underlying liver disease.

Careful observation and cessation of OCPs is warranted in women taking OCPs with hepatic adenomas less than 5 cm in size (Fig. 57-9). Although some groups have reported adenoma regression with cessation of OCPs, regression does not eliminate the risk of malignant transformation or hemorrhage. Therefore, reimaging should be performed within 6 to 12 months, and close observation is necessary.
The management of liver adenomatosis is primarily conservative. Close follow-up with either CT or MRI imaging and α-fetoprotein levels is indicated. Surgical resection should be reserved for nodules greater than 5 cm, large severely symptomatic nodules, or when malignancy cannot be excluded. In rare cases of large unresectable hepatic adenomas, liver transplantation may be indicated.

**Prognosis and Follow-Up**

Surgical resection can be performed safely and outcomes are excellent. Optimal surveillance and follow-up of hepatic adenomas remains controversial. For all adenomas, subtype classification should be attempted. Balabaud and colleagues have proposed a comprehensive algorithm for nodules less than 5 cm which addresses imaging, follow-up, and appropriate indications for resection.
MISCELLANEOUS BENIGN SOLID TUMORS

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a rare condition consisting of diffusely distributed hyperplastic hepatocyte lesions. NRH lesions are often associated with portal hypertension; however, these tumors lack a fibrous rim, thus differentiating them from liver cirrhosis. These lesions have no malignant potential and tumor growth is rare. NRH is typically multifocal and diffuse, which helps differentiate this lesion from hepatic adenomas, which are generally solitary lesions. With regard to FNH, NRH is similar in radiographic appearance; however, on portal venous phase CT scan, NRH typically has complete contrast washout, unlike FNH. Nonoperative management of NRH is indicated. In cases of diagnostic uncertainty, a tissue biopsy is warranted.

Bile Duct Adenoma

Bile duct adenomas are well-demarcated benign subcapsular lesions. Histologically, bile duct adenomas are lined by irregularly arranged cuboidal epithelium and mixed with variable amounts of stroma and inflammatory cells. Bile duct adenomas typically measure between 0.5 and 1 cm and are grossly well delineated with a gray-white appearance. These lesions are classically encountered incidentally, either radiologically, during exploration of the abdomen at the time of surgery for an unrelated reason, or at autopsy. Bile duct adenomas are considered proliferative/reactive lesions rather than neoplastic. Operative resection is seldom required and expectant management is justified.

Hepatic Hamartomas

Hepatic hamartomas are rare liver tumors of infancy, typically discovered before 2 years of age. Hepatic hamartomas comprise 8% of all pediatric tumors and consist of irregularly arranged and dysmorphic bile ducts mixed with myxomatous mesenchyme. Continued tumor growth results in
compression of adjacent structures that can lead to significant complications such as biliary obstruction, portal hypertension, and death. Although some hepatic hamartomas may involute spontaneously, malignant transformation is possible. Complete resection or enucleation is the standard of care. Fenestration or marsupialization is contraindicated given the propensity for local recurrence and malignant potential. Close observation may be warranted in specialized cases, particularly in patients whose hamartomas contain a dominant vascular component.\textsuperscript{71}

**Peliosus Hepatis**

Peliosus hepatis consists of multiple blood-filled sacs within the hepatic parenchyma. Peliosus hepatis lacks an epithelial lining, and recanalization and fibrosis are common.\textsuperscript{67} It occurs in immunocompromised patients, including patients taking anabolic steroids, AIDS patients, and transplant recipients.\textsuperscript{72,73} Tumor rupture and massive intraabdominal hemorrhage have rarely been reported.\textsuperscript{74} In these instances, angioembolization is the preferred treatment modality. Surgical resection is rarely indicated, and optimal management consists of minimizing identifiable etiologies, ie, steroid therapy.

**CONCLUSION**

With increasing utilization of cross-sectional imaging, benign liver lesions are increasingly encountered. As a result, it is imperative that clinicians gain an understanding of these lesions in order to appropriately manage these patients. The natural history and etiology of these lesions remains poorly defined; however, improved imaging technologies and renewed research interests have contributed significantly to our understanding of these lesions. For example, recent studies describing molecular pathogenesis have directly impacted diagnostic and management protocols, ie, hepatic adenoma subtype classification. Although management of most benign liver lesions typically consists of observation, certain lesions or characteristics are more prone to malignant transformation and/or complications and therefore warrant surgical resection. Future research should continue to elucidate the natural history of these lesions to better understand appropriate therapies and surveillance in
order to optimize patient outcomes.

ACKNOWLEDGMENTS

The authors wish to thank Drs. Ihab Kamel, Robert Anders, and Sepideh Bessharati for their invaluable contributions to this chapter.

REFERENCES


MALIGNANT LIVER NEOPLASMS

Sameer H. Patel • Guillaume Passot • Jean-Nicolas Vauthey

INTRODUCTION

In 2018, primary liver tumors will be diagnosed in approximately 42,220 new patients in the United States, and approximately 30,200 individuals will die from this disease.¹ Worldwide, primary liver tumors remain the second leading cause of death from cancer in males and the sixth leading cause of death from cancer in females.² Malignant lesions can arise from any of the various cell types that comprise the organ, which include hepatocytes, endothelial cells, and the cells of the intrahepatic bile ducts. The 2 most common hepatic neoplasms are hepatocellular carcinoma (HCC), which accounts for more than 75% of primary liver tumors, and intrahepatic cholangiocarcinoma (ICC), which accounts for 10% to 15%. The remaining primary hepatic neoplasms are hepatic angiosarcoma, epithelioid hemangioendothelioma, and hepatic lymphoma. The focus of this chapter will be on HCC and ICC.

In patients with primary hepatic malignancies, the malignancy itself and any underlying liver disease must be considered as 2 separate but
interconnected pathologic processes. The extent of abnormalities associated with each pathologic process directly affects the clinical impact and treatment options.

HEPATOCELLULAR CARCINOMA

Epidemiology

The incidence of HCC is greatest in areas where exposure to factors that cause chronic HCC injury is heaviest. The incidence of HCC is greatest in sub-Saharan Africa and East Asia, where the incidence is more than 20 cases per 100,000 individuals per year. In the United States, the overall incidence of HCC is 6 cases per 100,000 individuals per year; the incidence is highest among Asian, African American, and Hispanic individuals. Globally, males have up to 5.7 times the HCC incidence observed in females.

Risk Factors

There are several risk factors for development of HCC, many of them related to the development of chronic hepatocellular injury (Table 58-1). Some risk factors are independent, while others have potentiating effects. The risk factors most commonly observed in individuals with HCC are the hepatitis viruses: worldwide, 75% to 80% of primary liver tumors are associated with persistent liver infections, particularly hepatitis B (seen in 50%-55% of patients with HCC) or hepatitis C (25%-30%). The degree of liver change that results from hepatitis before development of HCC differs between hepatitis B and C. Among patients with hepatitis B, 20% of HCC cases develop before cirrhosis develops, whereas among patients with hepatitis C, HCC almost always arises in the background of significant cirrhosis and fibrosis. The mechanism proposed to explain this difference is that hepatitis B virus directly modulates oncogenes, whereas hepatitis C virus–induced HCC is related to the degree of inflammation.
Today, with vaccination against hepatitis B and better detection of hepatitis B and C, approximately 60% of patients with HCC are not infected with hepatitis virus. Other risk factors for HCC include environmental exposures, chronic disease processes, and genetic conditions that predispose patients to development of cirrhosis and/or chronic liver inflammation.

Alcohol consumption is a major risk factor for the development of HCC. Metabolism of alcohol occurs through oxidative processes, resulting in lipogenesis and fatty liver development that can progress to cirrhosis. Additionally, reactive oxygen species are created in hepatocytes during alcohol metabolism and can lead to further liver damage. The degree of alcohol-induced liver damage and related risk of HCC development are dose dependent. Studies have found that exposure to 60 g of alcohol per day for more than 25 years increases the risk of HCC by almost 6 times (odds ratio [OR], 5.7; 95% confidence interval [CI], 2.4-13.7).

Aflatoxin is a hepatic carcinogen produced by *Aspergillus flavus* and *Aspergillus parasiticus* that contaminates foods stored in warm and damp environments, such as corn, soybeans, and peanuts. The mycotoxin is thought to act by creating mutations in the *TP53* gene. Regions of the world where

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<tr>
<th>Hepatom-cellular Carcinoma</th>
<th>Intrahepatic Cholangiocarcinoma</th>
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<tr>
<td>Hepatitis B</td>
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</tr>
<tr>
<td>Hepatitis C</td>
<td>Cholelithiasis or hepatolithiasis</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Cholecystitis</td>
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<tr>
<td>Smoking</td>
<td>Choledochal cysts/Caroli disease</td>
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<tr>
<td>Aflatoxin exposure</td>
<td>Thorotrust contrast agent exposure</td>
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<tr>
<td>Vinyl chloride exposure</td>
<td>Hepatitis B</td>
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<tr>
<td>Oral contraceptive pill use</td>
<td>Hepatitis C</td>
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<tr>
<td>Diabetes</td>
<td>Diabetes</td>
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<tr>
<td>Nonalcoholic fatty liver disease (nonalcoholic steatohepatitis)</td>
<td>HIV infection</td>
</tr>
<tr>
<td>Hereditary hemochromatosis</td>
<td><em>Opisthorchis sinensis</em> infection</td>
</tr>
<tr>
<td>α₁-Antitrypsin deficiency</td>
<td><em>Opisthorchis viverrini</em> infection</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Lynch syndrome</td>
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</table>
Aflatoxin exposure is highest coincide with regions of high hepatitis B prevalence, and the effects are potentiative. A study has found that individuals in Shanghai with concomitant hepatitis and aflatoxin exposure had 59.4 times the risk of developing HCC of the normal population. Hepatitis B alone was associated with only a seven-fold increase in risk, whereas aflatoxin exposure alone was associated with a four-fold increase in risk.9

Higher body mass index (BMI) has been associated with increased death rates from multiple malignances, including esophagus, colorectal, pancreas, and liver cancers. Women with a BMI of 35 to 40 kg/m² had almost twice the mortality rate from liver cancer of women with a lower BMI, and men with a BMI of 35 to 40 kg/m² had almost 5 times the liver cancer mortality rate of men with a lower BMI.10 Obesity can lead to the development of chronic liver changes, such as steatosis and steatohepatitis.11 Obesity in the United States affects over 1 in 3 adults.10

**Protective Factors**

Statin use has been found to protect against the development of HCC. A meta-analysis of 10 studies with 1.46 million patients found that statin use was associated with an adjusted OR of 0.63 (95% CI, 0.52-0.76).12 Despite the heterogeneity of the studies analyzed in this meta-analysis, this protective affect was seen not only in Asian but also in Western populations. Statins are thought to inactivate pro-growth pathways and activate apoptotic pathways through hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase-dependent and -independent pathways.12

Prevention of HCC is based on reduced exposure to the risk factors such as environmental exposures and hepatitis viruses. Vaccination against hepatitis B has reduced HCC rates in high-risk countries such as Taiwan.13 In patients with hepatitis B or C, close surveillance and treatment to prevent development of cirrhosis are of paramount importance and have been shown to improve outcomes associated with HCC.14

**Pathology**
HCC is thought to develop in a multistep progression from normal hepatocytes to malignancy (Fig. 58-1) through alterations in various molecular pathways. A consensus on the nomenclature for precancerous lesions and early HCC has been developed to standardized pathologic assessment of specimens. Dysplastic nodules are defined as nodular lesions larger than 5 mm. These are divided into low-grade and high-grade dysplastic nodules. Low-grade nodules have no cytologic atypia and often have a peripheral fibrous scar. High-grade nodules have architectural and/or cytologic atypia, increased cell density, and an irregular trabecular pattern. These lesions precede the development of HCC.

**FIGURE 58-1** Vascular and radiographic findings associated with progression from precancerous lesions to hepatocellular carcinoma (HCC). CT, computed tomography; Iso, isodense. (Used with permission from J. Shindoh, MD, Toranomon Hospital, Tokyo, Japan.)

Early HCCs are larger than dysplastic nodules and characterized by 5 parameters: (1) cell density more than twice that of the surrounding tissue, with an increased nuclear/cytoplasm ratio and irregular thin-trabecular pattern; (2) portal tracts within the nodule (intratumoral portal tracts); (3) a
pseudoglandular pattern; (4) diffuse fatty changes; and (5) unpaired arteries within the nodule.\textsuperscript{15} Despite these defining criteria, differentiation between high-grade dysplastic nodules and early HCC is challenging. One of the key distinguishing findings is the presence of stromal invasion in HCC.\textsuperscript{15}

**Gross Features**

HCC can exhibit any of several growth patterns and was eloquently categorized by Eggel in 1901 into 3 separate types.\textsuperscript{16,17} The *nodular* type is characterized by well-circumscribed nodules and the absence of extranodal extension or multinodularity and has the lowest frequency of spread.\textsuperscript{17} Large HCCs that occupy the majority of the liver parenchyma are defined as *massive* and are often seen in livers that do not have cirrhosis (Fig. 58-2). Massive HCCs have a higher propensity for lymph node and intrahepatic metastases than nodular HCCs.\textsuperscript{17} Finally, *diffuse* HCCs are characterized by multiple small lesions covering the liver and are almost always associated with hematogenous extrahepatic metastases.\textsuperscript{17} Additional poor prognostic features often seen in patients with HCC are invasion of the portal and hepatic vein or bile duct.\textsuperscript{18,19}

![FIGURE 58-2](image)  
**FIGURE 58-2** Gross pathologic specimen of a massive hepatocellular carcinoma. (Used with permission from J. Shindoh, MD, Toranomon Hospital, Tokyo, Japan.)
**Fibrolamellar HCC**

Fibrolamellar carcinoma is a distinctive variant of HCC, accounting for less than 5% of all HCC cases. Unlike traditional HCCs, fibrolamellar carcinomas are seen in younger patients, affect males and females equally, and are not associated with chronic liver inflammation such as hepatitis or cirrhosis. Fibrolamellar carcinomas are slow growing, present with abdominal pain or an abdominal mass, are often resectable, and consequently have a better prognosis; the 5-year overall survival after resection is 76%.

**Combined HCC and Cholangiocarcinoma**

Combined HCC and cholangiocarcinoma is a type of liver tumor that contains elements of both HCC and cholangiocarcinoma and accounts for less than 1% of all primary liver tumors. The pathogenesis is malignant transformation of hepatic progenitor cells with dual differentiation leading to formation of a lesion capable of bile production, trabecular growth, glandular structures, and intracellular mucin production. Five-year overall and disease-specific survival rates for patients with combined HCC and cholangiocarcinoma fall in between those for patients with HCC and those for patients with cholangiocarcinoma.

**Clinical Presentation and Diagnosis**

Unlike other malignancies, HCC often presents incidentally as patients are being followed for underlying liver disease or when there is enough tumor progression to cause a mass effect. Direct obstruction of the bile ducts can lead to obstructive jaundice; compression of the liver capsule can cause right upper quadrant pain; and bleeding from the tumor can cause anemia if the bleeding is minimal or severe hemorrhagic shock if the bleeding is major. Additional generalized constitutional symptoms of HCC include anorexia, weight loss, and malaise. In patients with cirrhosis in whom HCC is discovered incidentally, general physical examination findings caused by portal hypertension include ascites, jaundice, varices, and splenomegaly. Other, rarer presentations include development of fevers secondary to tumor necrosis and paraneoplastic syndromes such as hypoglycemia,
hypercalcemia, hypercholesterolemia, watery diarrhea, erythrocytosis, and cutaneous manifestations, which are present in multiple gastrointestinal malignancies but not necessarily specific for HCC (Table 58-2).25-28

### TABLE 58-2: PARANEOPLASTIC SYNDROMES ASSOCIATED WITH HEPATOCELLULAR CARCINOMA

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Underlying Mechanism</th>
</tr>
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</table>
| Hypoglycemia           | Increased metabolic activity  
------------------------|-----------------------|Insulin-like growth factor II secretion |
| Hypercalcemia          | Parathyroid hormone–related protein secretion  |
| Watery diarrhea        | Vasoactive intestinal polypeptide, gastrin, or prostaglandin activity  |
| Hypercholesterolemia   | Cholesterol dysregulation  |
| Erythrocytosis         | Erythropoietin secretion  |
| Thrombocytopenia       | Portal hypertension  |
| Cutaneous              | Cytokines secretion  |
| Seborrheic keratoses   |                       |
| Pityriasis rotunda     |                       |
| Dermatomyositis        |                       |
| Pemphigus foliaceus    |                       |
| Porphyria cutanea tarda|                       |

One of the unique features of HCC is its hypervascularity. HCC derives the majority of its blood supply from the hepatic artery as opposed to the portal vein.29 This feature allows accurate identification of HCC on imaging, particularly on high-quality multiphase (unenhanced, arterial phase, portal venous phase, and delayed venous phase) cross-sectional imaging. The pathognomonic radiographic profile is enhancement in the arterial phase followed by washout in the delayed venous phase (Fig. 58-3). Additional common findings are delayed enhancement of the fibrous pseudocapsule, presence of septations, and an internal mosaic pattern.
The decision whether to use computed tomography (CT) or magnetic resonance imaging (MRI) for diagnosis of HCC is largely dependent on the institution and the physician’s level of comfort with interpreting the results. A meta-analysis of 15 studies comparing CT to MRI found that MRI was associated with better sensitivity (91% vs 81%) and specificity (95% vs 93%), especially for smaller HCC lesions.\(^3\)\(^0\) Regardless of the modality used, if the lesion is larger than 1 cm and exhibits the classic appearance of HCC on radiographs, no additional workup or biopsy is needed for diagnosis. If the imaging findings are not definitive, the next step is repeat imaging with another modality (CT if MRI was used and vice versa). If the imaging findings remain ambiguous after repeat imaging, a needle biopsy can be performed unless the patient is a candidate for liver transplant. In candidates for liver transplant, biopsy should be avoided until evaluation by a transplant team to avoid peritoneal seeding even though the risk of seeding is low when needle biopsy is performed by a physician with appropriate experience. For lesions smaller than 1 cm, hepatic ultrasonography should be performed every 3 months.\(^3\)\(^1\) If there are concerning changes or findings, further investigation is warranted (Fig. 58-4).
Screening

Screening for HCC should be reserved for patients at high risk for development of HCC and should not be performed in the general population. Individuals with cirrhosis of the liver should undergo evaluation with liver sonography every 6 to 12 months according to the American Association for
The tumor marker most commonly used for monitoring and diagnosis of patients at high risk for HCC is α-fetoprotein (AFP). AFP is a glycoprotein produced by the fetal liver and yolk sac. AFP can be elevated in a variety of disease processes and other malignancies, including tumors of gonadal origin, gastric cancer, pregnancy, acute or chronic hepatitis, and cirrhosis. Typically an AFP value of greater than 20 µg/L is considered abnormal, but with this cutoff value, there are significant variations in the sensitivity and specificity of AFP level according to the population examined (patients with cirrhosis or chronic hepatitis vs patients with normal livers). Therefore, the status of the underlying liver must be taken into account in interpreting the AFP level. Furthermore, up to 40% of patients with small HCCs have normal AFP levels.

Because AFP measurements alone have variable sensitivity and specificity in the diagnosis of HCC, imaging remains the mainstay of surveillance. The combination of characteristic imaging findings with an elevated AFP level does have high positive predictive value. In Japan, where the prevalence of HCC is much higher than in the United States, the Japanese Society of Hepatology recommends liver sonography and serum AFP and plasma des-gamma-carboxy prothrombin measurement every 3 to 4 months and CT or MRI every 6 to 12 months for patients with cirrhosis related to hepatitis B or C. For patients with chronic hepatitis B or C or with cirrhosis not due to hepatitis B or C, the Japanese Society of Hepatology recommends liver sonography and serum AFP and plasma des-gamma-carboxy prothrombin measurement every 6 months with or without cross-sectional imaging when such imaging would be appropriate.

**Staging**

The treatment of HCC involves consideration of 2 separate pathologic processes, the primary liver tumor and any underlying liver disease. To help stratify patients for treatment, there are 2 general systems of staging, pathologic and clinical. The pathologic staging systems are based on surgical outcomes and include the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system, Liver Cancer Study Group of Japan staging system, Japanese Integrated Staging score, and
The clinical systems include the Okuda system, Cancer of the Liver Italian Program (CLIP) scoring system, and Barcelona Clinic Liver Cancer (BCLC) staging system.

The seventh edition of the AJCC/UICC staging system (Table 58-3) takes into account prognostic factors after resection of HCC, including tumor size (cutoff 5 cm), solitary versus multiple tumors, and presence or absence of vascular invasion. The most important prognostic factor is vascular invasion. Tumors without vascular invasion are defined as T1; those with vascular invasion as at least T2; and those with major vascular invasion, defined as invasion of a major branch of the portal or hepatic vein, as T3. Five-year overall survival rates after liver resection for patients with stages I, II, and III HCC are 55%, 37%, and 16%, respectively (Fig. 58-5).
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<td>T1</td>
<td>Solitary tumor ≤2 cm, or &gt;2 cm without vascular invasion</td>
</tr>
<tr>
<td>T1a</td>
<td>Solitary tumor ≤2 cm</td>
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<td>T1b</td>
<td>Solitary tumor &gt;2 cm without vascular invasion</td>
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<td>T2</td>
<td>Solitary tumor &gt;2 cm with vascular invasion, or multiple tumors, none &gt;5 cm</td>
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<tr>
<td>T3</td>
<td>Multiple tumors, at least one of which is &gt;5 cm</td>
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<tr>
<td>T4</td>
<td>Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum</td>
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<td>M0</td>
<td>IA</td>
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<td>IIIB</td>
</tr>
<tr>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVB</td>
</tr>
</tbody>
</table>

FIGURE 58-5 Survival after liver resection for hepatocellular carcinoma according to stage. Stage I, single tumor without vascular invasion. Stage II, single tumor with vascular invasion or multiple tumors, none >5 cm. Stage III, multiple tumors, any >5 cm, or single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein. (Reproduced with permission from Vauthey JN, Lauwers GY, Esnaola NF, et al: Simplified staging for hepatocellular carcinoma, J Clin Oncol 2002 Mar 15;20(6):1527-1536.)

Although there were significant improvements between the sixth and seventh editions of the AJCC/UICC staging system, additional stratification of the current stage categories may lead to better assessment of patient prognosis. An international multicenter study showed that neither microvascular invasion nor tumor differentiation affects surgical outcomes in patients with HCCs smaller than 2 cm. This subset of patients can be reclassified into a separate group that is associated with improved prognosis. Evaluation of the underlying liver disease is assessed through a fibrosis score, which is stratified into 2 tiers. Although this score is not incorporated into the overall staging, it does provide prognostic value with respect to overall survival, as patients with associated liver disease have a worse prognosis.
Clinical staging systems are more useful than pathologic staging systems for choosing the appropriate treatment regimen, particularly when surgery is not feasible. The Okuda system (Table 58-4) is based on tumor size, presence of ascites, albumin level, and bilirubin level and categorizes patients into 3 stages.\textsuperscript{50} Unfortunately, the Okuda system was derived from a cohort with primarily advanced HCC and used limited tumor-specific factors. As a result, it has little validity in patients with early HCC and groups patients with vascular invasion and multifocal disease into a single group.

| TABLE 58-4: OKUDA STAGING SYSTEM FOR HEPATOCELLULAR CARCINOMA\textsuperscript{50} |
|-----------------|-----------------|-----------------|
| **Criterion**   | **Positive**    | **Negative**    |
| Tumor size      | ≥50% of liver   | <50% of liver   |
| Ascites         | Clinically detectable | Clinically absent |
| Albumin level   | ≤30 g/L         | >30 g/L         |
| Bilirubin level | >3 mg/dL        | <3 mg/dL        |

**Stage Definition**

I No criterion positive
II 1 or 2 criteria positive
III 3 or 4 criteria positive


The CLIP scoring system (Table 58-5) is based on the Child-Turcotte-Pugh (CTP) score (Table 58-6), tumor morphology, serum AFP level, and presence or absence of portal vein thrombosis.\textsuperscript{51} Although the CLIP system stratifies patients with respect to prognosis better than the Okuda system does, the CLIP system still groups a wide range of patients with heterogeneous outcomes together and does not accurately account for vascular invasion.\textsuperscript{43}
### TABLE 58-5: CANCER OF THE LIVER ITALIAN PROGRAM SCORING SYSTEM FOR HEPATOCELLULAR CANCER

**Variable** | **Score**
--- | ---
Child-Turcotte-Pugh Stage |  |
A | 0 |
B | 1 |
C | 2 |

**Tumor Morphology**

| |  |
--- | ---
Uninodular and extension ≤50% | 0 |
Multinodular and extension ≤50% | 1 |
Massive or extension >50% | 2 |

**α-Fetoprotein Level, units ng/mL**

| |  |
--- | ---
≤400 | 0 |
≥400 | 1 |

**Portal Vein Thrombosis**

| |  |
--- | ---
Absent | 0 |
Present | 1 |

Overall score is the sum of the scores for the 4 individual variables. Median survival for scores of 0, 1, 2, 3, and 4-6 was 36, 22, 9, 7, and 3 months, respectively. Adapted with permission from Daniele B, Annunziata M, Barletta E, et al: Cancer of the Liver Italian Program (CLIP) score for staging hepatocellular carcinoma, *Hepatol Res* 2007 Sep;37 Suppl 2:S206-S209.

### TABLE 58-6: CHILD-TURCOTTE-PUGH (CTP) SCORE
The BCLC staging system (Fig. 58-6) was designed to incorporate more prognostic factors and better stratify patients with early HCC. The system created 5 stages based on the primary tumor size and number of nodules, liver function, performance status, presence of constitutional symptoms, vascular invasion, and extrahepatic spread. Limitations of this system include lack of a patient-centered approach, failure to outperform other systems in larger studies, and relatively few patients judged to be candidates for resection or interventional therapy. In Figure 58-6, candidates for resection according to the BCLC staging system are highlighted in red.
In selecting among the multitude of available HCC staging systems, physicians should take a patient-centered approach. The AJCC/UICC pathologic staging system should be used for patients who undergo resection. It remains the only system validated in independent cohorts of patients undergoing either hepatic resection or transplant. In contrast, patients with advanced HCC with poor liver function have a better assessment of prognosis with clinical staging systems, particularly the BCLC system.

**CTP Score**

Hepatic functional reserve, the most important predictor of mortality risk, is determined by using the CTP score (Table 58-6). This score is based on the grade of encephalopathy, presence or absence of ascites, serum bilirubin level, serum albumin level, and prothrombin time and is used to stratify...
patients into 3 groups with different risk. The CTP score has been validated in multiple studies and is incorporated into various treatment algorithms for hepatic neoplasms. Early studies showed that the perioperative mortality rates associated with abdominal operations in patients with CTP class A, B, and C disease were 10%, 30%, and 82%, respectively. In light of these risks, patients with CTP class A HCC and selected patients with class B HCC can undergo liver resection without significant complications. In contrast, patients with HCC with CTP class C disease have extremely high perioperative mortality rates and should not undergo resection if it can be avoided.

**Treatment**

Determining the appropriate therapy for patients with HCC can be challenging. Multiple factors need to be taken into account, including patient performance status, liver quality, and tumor burden. With appropriate patient selection, studies have demonstrated 5-year overall survival rates of up to 70%.

For patients without underlying liver disease and resectable disease, liver resection offers the best survival, and for patients with underlying liver disease, liver transplant offers the best prognosis. Patients with poor liver function who are not candidates for transplant should proceed with supportive care, systemic therapy, or liver-directed therapies.

**SURGERY**

The first decision is to decide whether the lesion is resectable, which depends on the extent of extrahepatic disease. Many would consider vascular invasion, involvement of adjacent organs besides the gallbladder, extension beyond the visceral peritoneum, or disease in multiple nodes (AJCC seventh edition stage IIIb or greater) to render HCC unresectable. However, exceptions can be made for selected patients when care is undertaken by a multidisciplinary team at a high-volume center.

If HCC is judged resectable, the status of the underlying liver needs to be assessed. Patients with poor liver quality should be referred for transplant, while those with acceptable liver quality (CTP class A or B) should be
optimized medically. Table 58-7 summarizes criteria for resection in patients with chronic liver disease at the University of Texas MD Anderson Cancer Center.\textsuperscript{59}

### TABLE 58-7: THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER CRITERIA FOR RESECTION IN CHRONIC LIVER DISEASE

<table>
<thead>
<tr>
<th>Type of Resection</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Minor (≤3 liver segments) | Child-Turcotte-Pugh class A  
Bilirubin level ≤20 g/L  
Absence of ascites  
Platelet count >1 × 10^6/L |
| Major (>3 liver segments) | Criteria for minor resection plus:  
Bilirubin level ≤1 mg/dL  
Absence of portal hypertension  
Portal vein embolization in patients with future liver remnant <40% |


Patients with an inadequate future liver remnant should undergo portal vein embolization (PVE). PVE in patients with HCC can increase the future liver remnant (Fig. 58-7), thereby increasing the number of patients eligible for resection, reducing liver failure–related complications, and increasing the safety of liver resection.\textsuperscript{60-62} Generally, for safe liver resection, patients without liver disease need a minimum future liver remnant of at least 20%, patients who underwent chemotherapy need a future liver remnant of at least 30%, and patients with cirrhosis or fibrosis require a future liver remnant of at least 40%.\textsuperscript{63-65} PVE, similar to functional liver tests such as indocyanine green clearance and technetium-99m-galactosyl human serum albumin scintigraphy, is able to provide information about the severity of liver disease. Degree of liver hypertrophy less than 5% at 3 weeks after PVE is associated with increased risk of liver-related complications, hepatic dysfunction or insufficiency, prolonged hospital stay, and 90-day mortality.\textsuperscript{66} Table 58-8 summarizes indications and contraindications for PVE.\textsuperscript{60}
FIGURE 58-7  Right portal vein embolization (PVE) and segment IV embolization for a large hepatocellular carcinoma. A. Pre-PVE computed tomography (CT) scan. Standardized future liver remnant (sFLR) (segments I, II, and III, outlined in blue) = 12%. B. CT scan 3 weeks after right PVE and segment IV embolization. sFLR = 22%, and degree of hypertrophy = 10%. C. CT scan 8 years after extended right hepatectomy. sFLR = standardized future liver volume measured on CT/standardized total liver volume. Standardized total liver volume = $-794.41 + 1267.28 \times \text{body surface area (m}^2\).
TRANSPLANT

For patients with HCC who have significant underlying liver dysfunction that precludes resection because of the risk of liver-related complications, liver transplant is an option. To determine who is a candidate for liver transplant, the United Network for Organ Sharing (UNOS) uses the Milan criteria, proposed by Mazzaferro and colleagues: solitary lesion smaller than 5 cm or up to 3 lesions all smaller than 3 cm with absence of extrahepatic disease or vascular invasion. Patients meeting these criteria achieved 4-year survival rates of 75%. Patients with CTP class B or C disease who meet the Milan criteria are best treated with transplant, while patients with CTP class A disease often go straight to resection. However, the recurrence rate after liver resection has been reported to be up to 70%.

A group at the University of California San Francisco (UCSF) proposed expansion of the UNOS criteria to single tumors no larger than 6.5 cm or a maximum of 3 tumors, none larger than 4.5 cm and with the sum of the maximum diameters of the tumors no greater than 8 cm. This proposed expansion is controversial because 5-year overall survival rates of patients who met these criteria and underwent transplant ranged from 38% to 93%.
The data remain unclear regarding the suitability of the UCSF criteria. Proponents of the UCSF criteria state that patients with larger HCCs can be cured with transplant, while critics cite higher rates of vascular invasion and recurrence. Given the relative shortage of livers, the UNOS criteria remain the standard in the United States.67,69,71

**LOCOREGIONAL THERAPIES**

Several locoregional therapies exist for patients with HCC who are not candidates for resection or transplant. These include radiofrequency ablation (RFA), percutaneous ethanol injection, and transarterial chemoembolization (TACE). RFA uses application of radiofrequency energy with an alternating current to cause thermal damage to tissues. The range of tissue damage from RFA suggests that the optimal candidates for RFA are those with tumors smaller than 2 cm if RFA is delivered with curative intent and tumors smaller than 4 cm if RFA is delivered with palliative intent. Randomized controlled trials comparing RFA and percutaneous ethanol injection found that RFA was associated with better overall survival.74

Characteristically, HCC derives its blood supply from the hepatic artery. TACE capitalizes on this fact and involves injection of chemotherapeutic agents with a procoagulant material into the hepatic artery branch supplying the tumor. TACE has been proven to be more effective than supportive care.75,76 Drug-eluting polyvinyl alcohol microspheres or beads can also be injected into the tumor, resulting in embolization and local administration of chemotherapy to the lesion and limiting the escape of chemotherapeutic agents.

TACE is often used for large HCCs that are not amenable to resection or ablation. Chemotherapeutic agents commonly used for TACE are doxorubicin, cisplatin, epirubicin, and doxorubicin-eluting beads. Randomized controlled trials comparing various chemotherapeutic agents have found no differences in outcomes, and the benefit of drug-eluting beads remains controversial.77,78 Locoregional therapies are often used as a bridge to transplant, particularly when patients are on the waiting list and their HCC lesion or lesions are close to exceeding the tumor size criteria. Many of the studies showing survival benefits from locoregional therapies had small numbers of patients, but use of such therapies is increasing at transplant centers throughout the United States.79
SYSTEMIC THERAPY

For patients with unresectable or metastatic HCC, systemic therapy is the primary treatment. HCC is notoriously resistant to cytotoxic chemotherapies given its overexpression of drug-resistance genes. Furthermore, patients with HCC often have underlying liver dysfunction that causes cytotoxic chemotherapies to be poorly tolerated. Sorafenib has emerged as the standard systemic therapy option for advanced HCC. Sorafenib is a multikinase inhibitor acting on vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, FLT3, Raf-1, Ret, and c-Kit. Two randomized phase III trials, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and the Asia-Pacific trial, demonstrated statistically significant improvements in overall survival, of 2.8 months and 2.3 months, respectively, for patients with advanced HCC treated with sorafenib.\textsuperscript{80,81}

Despite the limitations of cytotoxic chemotherapy for HCC, modest effects are seen with combinations of different cytotoxic agents, particularly in patients with minimal underlying liver disease. The combination of cisplatin, interferon α-2b, doxorubicin, and fluorouracil (PIAF) showed an improvement of the objective response rate.\textsuperscript{82} The objective response rate increased with the number of cycles (Fig. 58-8), and for patients amenable to surgery after treatment with PIAF, survival was significantly improved compared to the survival of patients who were not able to undergo surgery after treatment with PIAF (Fig. 58-9)\textsuperscript{83}. 
FIGURE 58-8  Objective response rate according to number of cycles of cisplatin, interferon α-2b, doxorubicin, and fluorouracil (PIAF). (Reproduced with permission from Kaseb AO, Shindoh J, Patt YZ, et al: Modified cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma, Cancer 2013 Sep 15;119(18):3334-3342.)

FIGURE 58-9  Overall survival for patients with initially unresectable hepatocellular carcinoma according to whether patients received conventional or modified cisplatin, interferon α-2b, doxorubicin, and fluorouracil (FU) (PIAF) regimen and whether patients underwent surgery. Conventional PIAF:
cisplatin 80 mg/m² day 1, interferon α-2b 5 MU/m² days 1-4, doxorubicin 40 mg/m² day 1, and FU 500 mg/m² over 24 hours days 1-4. Modified PIAF: cisplatin 20 mg/m² days 1-4, interferon α-2b 4 MU/m² days 1-4, doxorubicin 40 mg/m² day 1, and FU 400 mg/m² as a bolus infusion on days 1-4. (Reproduced with permission from Kaseb AO, Shindoh J, Patt YZ, et al: Modified cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma, Cancer 2013 Sep 15;119(18):3334-3342.)

METHODS TO INCREASE RESECTABILITY OF LARGE HCC

Treatment of patients with good liver function, good performance status, and large HCCs who do not meet the criteria for transplant is challenging. For resectable HCC, recent series indicate that surgery performed by experienced surgical teams is associated with improved long-term survival (Fig. 58-10). Furthermore, for selected patients with BCLC stage B or C disease, resection can be proposed (Fig. 58-11). However, most patients with large HCCs have borderline resectable tumors at the time of diagnosis because of either a small future liver remnant or major vascular invasion.

FIGURE 58-10 Improvement in overall survival (OS) after major hepatectomy (resection of >3 liver segments) for hepatocellular carcinoma over time (n = 630). (Reproduced with permission from Andreou A, Vauthey JN, Cherqui D, et al. Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy, J Gastrointest Surg 2013 Jan;17(1):66-77.)
For patients with a small future liver remnant, PVE can be considered to increase resectability. The combination of PVE with TACE has been suggested to increase the rate of hypertrophy, especially for patients with underlying liver disease, by suppressing arterioportal shunts and increasing parenchymal damage in the embolized liver (Fig. 58-12). A sequential approach, with TACE completed 3 to 4 weeks before PVE, was associated with an increase of future liver remnant size and longer recurrence-free and overall survival compared to PVE alone. In patients without hepatitis or cirrhosis with tumors that were borderline resectable because of locoregional extension, PIAF also increased resectability. Figure 58-13 summarizes the treatment strategy for large HCCs advocated at MD Anderson Cancer Center. Treatment of patients by an expert multidisciplinary team optimizes the strategy and improves the outcome of patients with HCC (Fig. 58-14).
FIGURE 58-12  Intraoperative view of the liver in a patient with cirrhosis secondary to chronic hepatitis B and hepatitis C before right hepatectomy for hepatocellular carcinoma. After ligation of the right artery, the liver is demarcated along the main plane (Cantlie line). The patient underwent sequential transarterial chemoembolization followed by portal vein embolization prior to resection, and major hypertrophy of the left liver is clearly noticeable. The patient had a recurrence 4 years after liver resection and underwent salvage liver transplant. At this writing, the patient is alive 10 years after liver transplant.
FIGURE 58-13  Treatment strategy for large hepatocellular carcinoma at the University of Texas MD Anderson Cancer Center. Borderline resectability indicates insufficient future liver remnant or locoregional extension. PIAF, cisplatin, interferon α-2b, doxorubicin, and fluorouracil; PS, performance status; PVE, portal vein embolization; TACE, transarterial chemoembolization.
FIGURE 58-14 Management of a central large hepatocellular carcinoma (HCC) arising in a normal liver. A and B. Borderline large HCC involving hepatic hilum, left hemiliver, and right paramedian sector and abutting the right hepatic vein. C and D. After 3 months of sorafenib, the HCC remains borderline resectable. E and F. After 7 cycles of cisplatin, interferon α-2b, doxorubicin, and fluorouracil, the HCC is resectable. G. After right portal vein embolization. H. Twelve months after right hepatectomy, there is no evidence of disease.

INTRAHEPATIC CHOLANGIOCARCINOMA
Epidemiology

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver tumor following HCC and accounts for approximately 10% to 15% of primary liver malignancies. ICCs arise from the intrahepatic biliary tree and behave differently than extrahepatic cholangiocarcinomas (perihilar and distal cholangiocarcinomas). The incidence of ICC in the United States from 2000 through 2009 was 0.88 cases per 100,000 individuals per year, and the incidence continues to rise. The reason for this increase is unclear, but it is thought to be due to increased detection as a result of better diagnostic modalities and increases in the risk factors associated with ICC development. Unfortunately, most patients with ICC present with advanced disease, and the 5-year overall survival rate is only 5% to 10%; even with resection, the 5-year overall survival rate is a dismal 20% to 35%. Given the rarity of ICC, routine screening is not currently recommended.

Risk Factors

Risk factors for the development of ICC include conditions that lead to increased inflammation of the biliary tract (Table 58-1). Primary sclerosing cholangitis is an inflammatory condition of the biliary tract that leads to fibrosis and strictures. Almost 1 in 3 patients with cholangiocarcinoma are diagnosed with primary sclerosing cholangitis, and the lifetime risk of developing cancer in patients with primary sclerosing cholangitis is up to 15%. Congenital abnormalities of the biliary tree, such as choledochal cysts and Caroli disease, are associated with a 15% risk of developing cholangiocarcinoma. Infection with the liver flukes *Opisthorchis viverrini* and *Opisthorchis sinensis*, which are found in Asia, leads to chronic inflammation of the biliary system after the worms lay eggs in the biliary tree. Additional risk factors for ICC include cholelithiasis, hepatolithiasis, cholecystitis, exposure to Thorotrust contrast agent, hepatitis B and hepatitis C, and Lynch syndrome.

Clinical Presentation and Diagnosis
Unlike extrahepatic cholangiocarcinomas, ICCs often present as an incidental mass on imaging rather than as a biliary obstruction. If the mass is large or pushing on the liver capsule, it can cause vague right upper quadrant pain or constitutional symptoms.

The workup begins with liver function studies, tumor marker studies, and cross-sectional imaging. Carcinoembryonic antigen and carbohydrate antigen 19-9 (CA 19-9) are the tumor markers most often used, and of these, CA 19-9 has the higher specificity. Studies have found that CA 19-9 level greater than 100 U/mL has a sensitivity of 53% and a specificity of up to 90% in the detection of ICC. Care must be taken when interpreting CA 19-9 levels in a patient with hyperbilirubinemia as the results can be falsely elevated. Unlike HCC, ICC has no pathognomonic radiologic characteristics; therefore, biopsy of the mass is required.

Early surgical evaluation is essential to determine whether the mass is a resectable and whether the patient is a candidate for transplant. No delay should be taken to refer the patient, even to acquire a biopsy. Care must be taken to ensure that the lesion is not a metastasis from another malignancy and that there is no disease outside the liver. The surgical workup entails performing an esophagogastroduodenoscopy and colonoscopy to rule out the presence of primary tumor outside the liver.

**Pathology**

The Liver Cancer Study Group of Japan classified ICC into 3 subtypes based on gross appearance: mass forming, periductal infiltrating, and intraductal growth (Fig. 58-15). The mass-forming type is the most common type, accounting for 85% of ICCs. On CT, mass-forming cholangiocarcinomas are homogeneous with low attenuation and peripheral enhancement (Fig. 58-16). On MRI, they are hypointense on T1-weighted images and hyperintense in the T2 phase. Periductal-infiltrating ICCs grow along the bile duct without forming a mass. Intraductal growth ICCs, as the name implies, grow within the bile duct and can appear as duct ectasia with or without a mass, a polypoid mass, an intraductal cast, or an intraductal stricture.
FIGURE 58-15 Subtypes of intrahepatic cholangiocarcinoma. (Used with permission from J. Shindoh, MD, Toranomon Hospital, Tokyo, Japan.)
FIGURE 58-16 Intrahepatic mass-forming type cholangiocarcinoma. A. Gross pathologic specimen. B. Contrast-enhanced computed tomography
Staging

Like staging for HCC, staging for ICC changed with the seventh edition of the AJCC/UICC staging system. ICCs, hilar cholangiocarcinomas, and distal cholangiocarcinomas were separated into different staging and are now able to better predict survival. For ICC, the system focuses on the number of tumors (1 or >1) and the presence or absence of vascular invasion and lymph node involvement (Table 58-9). The staging system was externally validated by the French Surgical Association ICC 2009 study group. After a mean follow-up interval of 34 months, median survival for patients with stage I ICC had not been reached; median survival was 53 months ($P = .01$) for patients with stage II disease and 16 months ($P < .0001$) for patients with stage III disease.  

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**TABLE 58-9: AMERICAN JOINT COMMITTEE ON CANCER/INTERNATIONAL UNION AGAINST CANCER STAGING SYSTEM FOR INTRAHEPATIC CHOLANGIOCARCINOMA, SEVENTH EDITION**
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</tr>
<tr>
<td>T1b</td>
<td>Solitary tumor &gt;5 cm without vascular invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor perforating the visceral peritoneum</td>
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<tr>
<td>T4</td>
<td>Tumor involving local extrahepatic structures by direct invasion</td>
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<td>IB</td>
</tr>
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<tr>
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<td>Any N</td>
<td>M1</td>
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</table>

Treatment

SURGERY

Surgery remains the only curative option for patients with ICC. Unfortunately, the majority of patients present with advanced disease that precludes resection. Depending on the location of the lesion, surgery involves resection of the liver involving the mass with negative margins, possibly resection of a portion of the extrahepatic bile ducts, and resection of regional lymph nodes. A multi-institutional study from the Italian Intrahepatic Cholangiocarcinoma Study Group found improved 5-year overall survival and recurrence-free survival when margins were negative. The size of the margin, however, did not predict outcome. In another international multi-institutional study, lymph node involvement was found in 30% of patients undergoing a formal lymphadenectomy and was associated with poor prognosis. In light of these findings, a portal lymph node dissection is warranted as it provides staging and prognostic information.

TRANSPLANT

Liver transplant for ICC remains controversial. The Mayo Clinic published their experience using neoadjuvant chemoradiotherapy followed by orthotopic liver transplant for unresectable cholangiocarcinoma arising in patients with primary sclerosing cholangitis and found a 5-year overall survival rate of 82%. In an intent-to-treat analysis from the Mayo Clinic and other centers, 5-year overall survival rates after orthotopic liver transplant were 53% to 55% with a high recurrence rate. Given these data, orthotopic liver transplant for ICC is currently performed only in highly selected patients at specialized transplant centers and should be done under a research protocol.

SYSTEMIC THERAPY

Systemic cytotoxic chemotherapy plays a greater role in the treatment of ICC than in the treatment of HCC. The Advanced Biliary Cancer Trial 02 was a phase III randomized controlled trial comparing gemcitabine plus cisplatin
versus gemcitabine alone in patients with advanced biliary tract cancers (ICCs, hilar cholangiocarcinomas, distal cholangiocarcinomas, ampullary adenocarcinomas, and gallbladder carcinomas). The results showed an improvement in overall survival (11.7 months vs 8.1 months) and progression-free survival (8 months vs 5 months) with the combination regimen. Consequently, gemcitabine with cisplatin is considered the standard of care for patients with advanced cholangiocarcinoma. Patients who undergo surgery and who have positive margins, node-positive disease, or adverse prognostic markers are offered fluoropyrimidine- or gemcitabine-based chemotherapy as adjuvant chemotherapy after surgery.

HEPATIC ANGIOSARCOMA

Hepatic angiosarcoma is the most common primary sarcoma arising from the liver. Hepatic angiosarcoma is a high-grade vascular neoplasm arising from malignant transformation of hepatic endothelial cells. About 200 cases are diagnosed annually worldwide, incidence is highest in patients older than 60 years, and most affected patients are male (male-to-female ratio, 3:1 to 4:1). Known risk factors for the development of hepatic angiosarcoma are exposure to vinyl chloride, thorotrast contrast agent, arsenic, and radium. Patients present with vague abdominal pain, malaise, nausea/vomiting, and abdominal distention from hepatomegaly or development of ascites. A rare presentation is tumor rupture leading to hemoperitoneum, which is associated with high morbidity and mortality. Treatment is centered around hepatic resection; however, over half of patients present with metastatic disease. For patients with unresectable disease, hepatic artery embolization can be employed for palliation. The prognosis for patients with hepatic angiosarcoma is dismal: in the absence of treatment, the majority of patients die within 6 months of diagnosis, and with treatment, only 3% of patients survive to 2 years.

EPITHELIOID HEMANGIOENDOTHELIOMA

Epithelioid hemangioendothelioma (EHE) is another rare tumor of mesenchymal origin. Classified as a low-grade malignant neoplasm, it arises from endothelial cells like hepatic angiosarcoma does. EHE is a disease of
middle-aged patients, and two-thirds of affected patients are females.$^{117,118}$ Patients present with abdominal pain and malaise, and if there is involvement of the hepatic veins, this can lead to Budd-Chiari syndrome.$^{119}$ Vinyl chloride exposure is thought to be one of the risk factors associated with development of EHE.$^{120}$ Resection remains the optimal treatment for EHE and is associated with 5-year overall survival rates of 75%.$^{121}$ Unfortunately, the majority of patients present with multifocal, diffuse disease that is not amenable to a hepatectomy. Orthotopic liver transplant is an option for patients with diffuse disease and is associated with 5- and 10-year survival rates of 83% and 74%, respectively.$^{122}$ Because EHE is indolent, patients can be followed to determine the biology of the tumor. Those who remain candidates for resection or orthotopic liver transplant can be stratified from patients with progression.$^{123}$ As with all rare diseases, large randomized studies of EHE are lacking. Multicenter investigations should be undertaken to better understand the biology and treatment options for patients with this disease.

**CONCLUSION**

Primary malignancies of the liver are difficult to treat because they are frequently advanced at diagnosis and frequently associated with chronic liver disease. With the recent expansion of therapeutic options, treatment algorithms are becoming increasingly complex. In-depth knowledge of the disease in combination with treatment by a multidisciplinary team allows for patient-centered therapeutic approaches and contributes to optimal outcomes.

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TREATMENT OF HEPATIC METASTASIS

Sean M. Ronnekleiv-Kelly • Sharon M. Weber

OVERVIEW

Hepatic metastases to the liver are significantly more common than primary liver malignancy and comprise approximately 90% of hepatic malignancies. Each year, approximately 140,000 new cases of colorectal cancer (CRC) are diagnosed in the United States, with hepatic metastases complicating 10% to 25% of cases.\(^1,2\) Two-thirds of these patients die from their disease as a result of liver involvement.\(^2\) In addition, numerous other malignancies metastasize to the liver. For instance, approximately 50% of patients with uveal melanoma develop liver metastases within 2 to 5 years after initial diagnosis, and 90% of metastatic uveal melanoma patients die with disease burden in the liver due to inefficacious systemic chemotherapy.\(^3\) Neuroendocrine tumors (NETs) also have propensity to metastasize to the liver as well as breast cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumors (GISTs), sarcoma, gynecologic and urologic malignancies, and melanoma.\(^4\) Therefore, because of the significant number of patients impacted by either primary or secondary liver malignancy, there is an
increasing need for effective locoregional therapy. Surgical resection as a part of multimodal therapy is generally considered the gold standard.\textsuperscript{5-8} However, resection is often not a reasonable option secondary to disease burden, tumor location, insufficient estimated future liver remnant, extrahepatic disease, and medical comorbidities. In fact, surgical resection for metastatic disease to the liver is only feasible in approximately 20\% of patients.\textsuperscript{9} Therefore, alternative options are necessary in the 60\% to 80\% of patients with metastatic disease to the liver in whom surgery is not possible.\textsuperscript{9} These nonresective techniques are the focus of this chapter.

**ARTERIAL-DIRECTED THERAPY**

Malignant tumors confined to the liver that cannot be addressed with curative intent are best treated with locoregional therapy. Primary liver lesions such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma as well as metastatic liver lesions such as colorectal, neuroendocrine, breast, melanoma, and renal can be palliated or down-staged with arterial-directed therapy. Transarterial directed therapy includes bland embolization, chemoembolization, drug-eluting beads (DEBs), and radioembolization. Bland embolization induces tumor ischemia by arterial disruption but does not use chemotherapeutic agents; therefore, tumor necrosis is simply accomplished by restricted blood supply. Chemoembolization, DEB, and radioembolization deliver toxic agents via the arterial system which preferentially supplies the tumor, in contrast to normal hepatocytes which derive much of their blood supply from the portal venous system.\textsuperscript{10} The latter three techniques are the focus of the arterial-directed therapy section.

**Transcatheter Arterial Chemoembolization**

**TECHNIQUE**

Transcatheter arterial chemoembolization also known as transarterial chemoembolization (TACE) was first introduced in 1980 for treatment of unresectable liver tumors, and since that time has expanded to include treatment of numerous malignant processes (HCC, neuroendocrine metastases, cholangiocarcinoma, melanoma, colorectal metastases).\textsuperscript{11}
Conceptually, liver tumors preferentially utilize hepatic arterial supply, and therefore chemotherapeutic agents with subsequent embolization can selectively target malignant cells while preserving surrounding liver parenchyma. Specific delivery of chemotherapeutic agents reduces systemic toxicity as the agents remain in the tumor bed; in addition, ischemia induced by arterial embolization can increase tumor cell lethality. However, preservation of proximal hepatic arterial inflow is essential to allow repeated treatments and the optimal number of treatments is based upon tumor response and hepatic reserve. Tumor response is characterized by reductions in size or lack of enhancement on CT/MRI indicating tumor necrosis.\textsuperscript{11}

After meticulous patient evaluation and characterization of tumor extent, femoral catheter insertion and subsequent angiography is utilized to delineate the vascular anatomy in the region of the tumor (Fig. 59-1A,B). The chemotherapeutic agent is then introduced into segmental or subsegmental vessels feeding the tumor(s). Variability in technique is common, including altering chemotherapeutic agents and embolic material, as well as inclusion of lipiodol, and also the technical selectivity of catheter positioning. Lipiodol is an iodinated ester from poppy seed oil that is combined with the chemotherapeutic mixture which allows emulsification of the drugs as well as directed targeting of liver tumors (Fig. 59-1C).\textsuperscript{11} The most common cytotoxic agents used include doxorubicin, gemcitabine, cisplatin, and mytomycin C (MMC). After delivery of chemotherapy agents, embolization is performed. Commonly used embolic agents include polyvinyl alcohol particles, starch microspheres, or gelfoam.\textsuperscript{11,12} Following embolization, angiography is performed, and subsequently cross-sectional imaging is obtained to confirm the interruption of blood supply.\textsuperscript{12} Patients generally require a short hospital stay post-procedure for intravenous hydration and pain control, as well as to monitor for post-embolization syndrome (discussed below). Additional TACE procedures can be performed at 4-week intervals until the specified tumor volume has been treated. Follow-up cross-sectional imaging is generally obtained at 1 month after completion of treatment to assess response; imaging is then obtained at 3-month intervals thereafter.\textsuperscript{13}
FIGURE 59-1 Conventional transcatheter arterial chemoembolization (TACE). (A) Contrast-enhanced CT images demonstrate a 9.1 × 8.8 cm heterogeneously enhancing mass in the right lobe of the liver in a female patient with metastatic leiomyosarcoma. (B) Digital subtraction angiography (DSA) anteroposterior view of a segmental right branch off the replaced right hepatic artery showing the hypervascular lesion. (C) Spot fluoroscopic image following conventional TACE demonstrates lipiodol deposition in the treated lesion.

OUTCOMES
Early randomized studies focused on TACE for unresectable HCC. Many did not demonstrate survival benefit of hepatic arterial chemoembolization versus more conservative treatment.\textsuperscript{14-19} However, more recent studies have identified a benefit in patients with unresectable HCC confined to the liver, and therefore TACE has emerged as a safe therapeutic option.\textsuperscript{20-22} Subsequently, metastatic disease to the liver has also been evaluated. Vogl and associates identified 463 patients with unresectable colorectal liver metastases (CRLM) that demonstrated no response or disease progression on systemic chemotherapy (two or more lines of chemotherapy), or developed toxicity precluding further systemic treatment. Therefore, all of the patients in the study received no further systemic chemotherapy. Patients received TACE comprised of MMC, MMC with gemcitabine, or MMC with irinotecan followed by embolization. The mean number of sessions was 5.3 per patient, and the TACE was tolerated quite well with minimal toxicity. Partial response (PR) was demonstrated in 14.7%, stable disease in 48.2%, and disease progression in 37.1% of patients according to the Response Evaluation Criteria in Solid Tumors (RECIST). Approximately 13% of patients achieved downstaging which allowed percutaneous ablative procedures to be performed. Median overall survival (OS) duration was 38 months from diagnosis of liver metastases and 14 months from initiation of chemoembolization; these survival times did not differ among the three TACE groups.\textsuperscript{23}

Albert and colleagues investigated TACE in 121 patients with metastatic CRC, most of whom had failed systemic chemotherapy for nonresectable CRLM. Chemoembolization consisted of MMC, doxorubicin, and cisplatin and was provided in 4-week intervals until the entirety of tumor volume had been treated (one cycle). Most procedure-related toxicity consisted of pain, fever, nausea, and emesis; serious complications occurred in 11% and included hepatic infarction, hematoma, pulmonary edema, myocardial infarction (MI), and venous thromboembolism (VTE). Overall, 2% had PR, 41% had disease stability, and 57% had disease progression (RECIST). Median time to progression was 5 months and median OS was 9 months after initiation of TACE. Median OS after diagnosis of liver metastases was 27 months, and the authors suggested that given the median survival was greater than historical survival of patients receiving systemic chemotherapy alone (ie, 20 months), chemoembolization provided an additive benefit to systemic chemotherapy.\textsuperscript{13}
Vogl and colleagues evaluated TACE followed by MR-guided laser-induced thermotherapy (LITT) for patients with CRLM (unresectable, inoperable, contraindications for surgery, or refusal of surgery). The mean number of TACE treatments was 3.7 and patients received MMC, MMC with gemcitabine, or MMC with irinotecan. PR was seen in 31% of patients with stable disease in 69%; overall mean reduction in tumor size was 21.4%. Reduction in tumor size was sufficient to allow LITT for all of the patients. Median time to progression was 8 months and median OS was 23 months. There was no difference between the treatment groups with respect to reduction in tumor size, response rate, time to progression, and OS. In addition, the treatments were well tolerated, with no mortalities or major complications. The authors concluded that the OS was favorable compared to previous studies demonstrating median survival between 10 and 20 months in patients with nonresectable CRLM receiving systemic or regional chemotherapy.

Use in liver metastases from noncolorectal primaries has also been demonstrated. Dong and Carr performed a retrospective study of TACE (doxorubicin or streptozotocin) in the treatment of unresectable metastatic NETs to the liver. An average of seven cycles was provided and PR was found in 62%, while 24% had minor response or disease stability. Median survival was about 3½ years, and the treatment was well tolerated. A recent analysis of therapeutic options for patients with gastro-enteric-pancreatic (GEP) NET identified TACE as a treatment modality for those with unresectable disease. However, the level of evidence presented was low and studies have failed to demonstrate an advantage of TACE over bland embolization.

Taken together, these investigations demonstrate marginal benefit at best for patients with CRLM undergoing TACE versus systemic chemotherapy. In addition, there have not been any robust studies demonstrating improvement in outcome utilizing TACE for CRLM. For these reasons, TACE is not currently recommended for treatment of colorectal liver metastases except as part of a clinical trial. Coincident with this, the European Neuroendocrine Tumor Society (ENETS) consensus guidelines for patients with GEP NET liver metastases stated that although symptom improvement occurs in 73% to 100% (duration 14-22 months) and CR/PR occur in approximately 33% to 50% of patients undergoing TACE for liver metastases from GEP NET, there
remains uncertainty whether TACE provides a survival advantage over systemic therapy.\textsuperscript{30}

**INDICATIONS**

Patients with good performance status and tumor suitable for resection, ablation, or transplantation should pursue curative measures. In patients with unresectable liver malignancy (primary or metastatic) and disease primarily confined to the liver, TACE can be utilized as salvage monotherapy when patients are unresponsive to systemic chemotherapy.\textsuperscript{12,13} TACE can also be used concordantly (neoadjuvant) with other treatment modalities such as LITT, radiofrequency ablation (RFA), microwave ablation (MWA), and resection. However, currently TACE appears to be best suited for treatment in patients with HCC (intermediate stage) as opposed to patients with liver metastases.\textsuperscript{31}

Congruent with the exclusion criteria for many of the above studies, contraindications to chemoembolization are absence of hepato-pedal flow and lack of compensatory collaterals, poor hepatic function (encephalopathy or ascites not controlled with diuretics), and biliary obstruction. Relative contraindications include poor hepatic synthesis (serum albumin <2 mg/dL), hepatic compromise (serum bilirubin >2 mg/dL, lactate dehydrogenase >425 U/L, aspartate aminotransferase >100 U/L), bleeding varices, ascites, thrombocytopenia, extensive tumor burden (>50% of liver), cardiac insufficiency, or renal insufficiency.\textsuperscript{10}

**COMPLICATIONS**

While TACE is generally well tolerated, complications include liver abscess (1%), tumor rupture (1%), acute liver failure, gastrointestinal bleeding (1%-4%), pulmonary embolism, renal dysfunction, cardiac toxicity, bile duct injury, bleeding from femoral puncture site (1%-2%), and post-embolization syndrome. This syndrome, which occurs in 4% to 10% of patients, is characterized by right upper quadrant pain, nausea, emesis, fever, and liver enzyme elevation.\textsuperscript{10,11} Although common, the syndrome typically resolves spontaneously within 7 to 10 days.
Drug-Eluting Bead Transarterial Chemoembolization

TECHNIQUE

Transcatheter delivery of agents such as doxorubicin and cisplatin has less systemic toxicity compared to standard systemic chemotherapy.\textsuperscript{32} Despite this, adverse effects such as acute liver failure, encephalopathy, ascites, upper GI bleeding, marrow suppression, alopecia, and renal failure still occur.\textsuperscript{10,11} Although TACE has demonstrated benefit for unresectable HCC, there remains a necessity for improved response rates and decreased complications which may allow expansion of indications. Localization of drugs specifically to the tumor with subsequent sustained release of the specific drug may result in decreased systemic effects and longer tumor exposure to the chemotherapeutic agent. By loading various chemotherapy agents onto polyvinyl alcohol-based hydrogel (DC-Beads, Biocompatibles, Surrey, UK) or a sodium acrylate and vinyl alcohol copolymer (HepaSphere, BioSphere Medical, Rockland, MA) and catheter delivery similar to standard TACE, drug-eluting bead transarterial chemoembolization (DEB-TACE) achieves directed delivery to the tumor microvasculature where the small compounds (100-300 mm and 300-500 mm, respectively) obstruct the vasculature.\textsuperscript{33} The lodged DEBs allow slow elution of chemotherapeutic agent in a sustained manner with prolonged exposure compared to TACE and lower systemic plasma levels of chemotherapeutic agent, resulting in reduced adverse effects.\textsuperscript{34,35} The technique is quite similar to TACE with the exception of the deployment of DEB microspheres impregnated with chemotherapeutic agent as opposed to chemotherapeutic agent with emulsificiant and embolic agent.\textsuperscript{36} Additional considerations include presence of replaced or aberrant vessels, avoidance of embolization of cystic artery, and evaluation of phrenic artery if suspected to supply the target tumor.\textsuperscript{37}

OUTCOMES

In the setting of CRLM, a phase III multi-institutional prospective randomized trial evaluated DEB loaded with irinotecan (DEBIRI) compared to systemic chemotherapy including folinic acid, 5-FU and irinotecan (FOLFIRI) in patients presenting with unresectable liver metastases from...
CRC (<50% liver parenchyma and no extrahepatic disease) who had undergone prior chemotherapy. Complete or partial response occurred in 69% of patients receiving DEBIRI compared to 20% of the systemic chemotherapy patients. At 2 years, survival was 56% in the DEBIRI group compared to 32% in the FOLFIRI group, and median OS was significantly higher in the DEBIRI group (22 months vs 15 months, \( p = .03 \)). Furthermore, neutropenia greater than or equal to grade III occurred in 4% of the DEBIRI population compared to 44% of the systemic population with fewer rates of diarrhea (6% vs 18%), alopecia (5% vs 35%), asthenia (20% vs 50%), and mucositis (1% vs 20%), indicating a superior safety profile. Supplementary data revealed improved quality of life scores and significant reduction in cost in the DEB-TACE patients compared to the patients receiving FOLFIRI.\(^{32}\) This study emphasized the importance of consideration of arterially directed therapy in select patients with metastatic disease to the liver.

INDICATIONS

The indications for DEB-TACE fall into the same category as for standard TACE; most studies have evaluated its use in HCC.\(^{37,38}\) DEB-TACE may provide survival benefit compared to systemic chemotherapy for CRLM; however, further studies are necessary to clarify this potential role.\(^{39}\)

COMPlications

Prajapati and colleagues sought to evaluate the safety and efficacy profile of small (100 to 300 mm) and large (300-500 mm) DEBs. DEB TACE with doxorubicin was performed in 94 patients (mean 2.8 per patient). Each group experienced similar mild complications (approximately 30%) consisting of abdominal pain (18%-26%), nausea (13%-17%), fever (3%-4%), and groin pain (3%-4%). The larger bead group had significantly more severe complications, including femoral artery pseudoaneurysm (1.7 vs 2.9%), prolonged hospitalization due to severe abdominal pain (1.7% vs 8.6%), and encephalopathy (0% vs 8.6%). Other complications included bradycardia (1.7%) and gastric ulceration/bleed (1.7%). In addition, mortality was 0% in the small bead group and 4% in the large bead group, leading the authors to conclude that 100 to 300 mm DEB may have an improved safety profile compared to larger beads.\(^{36}\)
Selective Internal Radiation Therapy

TECHNIQUE

Yttrium-90 (\(^{90}\text{Y}\)) radioembolization is a transarterial treatment for locoregional disease with demonstration of a clear palliative role by achieving delayed progression of hepatic lesions. Selective internal radiation therapy (SIRT) exploits the preferential arterial perfusion of hepatic malignant disease in order to expose liver lesions to radioactive microspheres. There are two microsphere forms that are commonly used including nonbiodegradable glass microspheres (TheraSphere\textsuperscript{TM}, MDS Nordion, Ottawa, Canada) of diameter 20 to 30 mm, and biodegradable resin microspheres (SIR-Spheres\textsuperscript{TM}, Sirtex, Lane Cove, Australia).\textsuperscript{10} As opposed to chemoembolization that combines chemotherapy and ischemia to achieve desired antitumor effect, \(^{90}\text{Y}\) radioembolization relies upon intravascular brachytherapy radiation effect to the targeted segment or lobe. The goal pulmonary exposure (pulmonary shunting) is less than 30 Gy while optimizing exposure to tumor.\textsuperscript{41} Prior to radioembolization of hepatic tumor, a simulation angiographic injection of 20 to 100 mm technetium-99m labeled albumin followed by single photon emission computed tomography (SPECT) imaging allows estimate of \(^{90}\text{Y}\) deposition (Fig. 59-2 A-D).\textsuperscript{40,41} The pretreatment simulation allows for projected tumor delivery as well as to evaluate for gastrointestinal (aberrant vessels) or pulmonary shunting (Fig. 59-2 E-G).\textsuperscript{41,42} Consequently, a tumor delivery dose can be estimated; however, tumor dose and resultant objective response is dependent upon tumor type, vascularity of the tumor (ie, intratumoral shunting), and use of previous systemic or intra-arterial agents.\textsuperscript{42} In addition, the targeted liver volume with associated feeding vessels can greatly influence the delivery dose. For instance, localized tumors confined within a specific segment can be targeted with the entire planned infusion of \(^{90}\text{Y}\) resulting in a “radiation segmentectomy” in which substantial doses are achieved (>1000 Gy).\textsuperscript{42} However, indications are not limited to segmental infusions, as lobar and whole-liver treatments are also routine and can be performed safely.\textsuperscript{33}
FIGURE 59-2 ⁹⁰Y radioembolization in a patient with multifocal hypervascular carcinoid metastases. (A) Early arterial and (B) delayed arterial phase digital subtraction angiography (DSA) images following selective right hepatic arterial injection. Note: The gastroduodenal artery has been prophylactically embolized to avoid non-target embolization of glass microspheres to the pancreaticoduodenal arcade. (C) Early arterial and (D) delayed-phase DSA images following selective left hepatic arterial injection in the same patient. Note arterial supply to segments II-IV as well as a small caudate artery coursing inferiorly off of the left hepatic artery (arrow). (E) 3D volumetric data is obtained from CT imaging performed during mapping angiography and used to facilitate dosimetric calculations for each lobar treatment. (F,G) Here, segmentation of the right hepatic lobe is used to calculate the volume of liver parenchyma perfused by the right hepatic artery.

Radioembolization is accomplished 1 to 2 weeks following the simulation. Femoral catheter cannulation and subsequent angiography is utilized to delineate the vascular anatomy in the region of the tumor. The selective
internal radiation therapy then consists of infusion of $^{90}\text{Y}$ loaded onto resin or glass microspheres. $^{90}\text{Y}$ is pure β-emission radiation and has a mean tissue penetration of 2.5 mm (maximum 10 mm) with a relatively short half-life of 64.1 hours. For this reason, isolation for radiation precaution is not required and the majority of radiation energy (97%) is emitted within the first 2 weeks. Although the absorbed dose is heterogeneous based on hemodynamics and tumor vasculature, the majority of the $^{90}\text{Y}$ is absorbed into the tumor compared to the normal liver parenchyma (3:1 to 20:1 ratio). The consequence of radiation exposure to tumor cells is irreversible cell damage. Patients are either observed in the hospital setting for a period of less than 24 hours or the procedure is performed on an outpatient basis. Follow-up imaging is then obtained at specified intervals in order to determine the response to therapy by RECIST criteria, World Health Organization (WHO) criteria, or European Association for the Study of Liver (EASL) criteria (Fig. 59-3). In the setting of downstaging or identifying tumor response based on size criteria alone, imaging can inadequately predict response as a result of discordance between residual size and cell viability. For example, in a study by Kulik et al. in patients with liver tumors treated with $^{90}\text{Y}$ who had tumor response allowing subsequent liver transplant, there was radiologic-pathologic discordance in five of seven patients receiving liver transplant. Imaging suggested viable tumor in each of the seven patients, while pathologic analysis demonstrated complete pathologic necrosis in five patients. Therefore, additional characteristics such as enhancement on CT or MRI, or PET imaging can be utilized to estimate tumor volume as defined by the modified RECIST assessment or the EASL guidelines assessing percent change in enhancing tissue.
FIGURE 59-3 ⁹⁰Y radioembolization treatment and follow-up imaging. (A) Contrast-enhanced CT demonstrates a 2.5 × 2.7 cm homogeneously enhancing NET metastasis in segment VIII. (B) Three-month and (C) 6-month post-contrast T1WI following ⁹⁰Y radioembolization confirm significant post-⁹⁰Y necrosis and volume reduction.

OUTCOMES

⁹⁰Y radioembolization has been evaluated in numerous studies and is currently recognized as a treatment option for unresectable Barcelona Clinic Liver Cancer (BCLC) intermediate stage HCC in the National Comprehensive Cancer Network guidelines.⁴⁰,⁴²-⁴⁴ Metastatic disease to the liver has also been demonstrated to respond to ⁹⁰Y therapy and is currently a category 3 recommendation for CRLM due to limited data in a highly select patient population.²⁹

In a single-institution analysis, Cianni et al. evaluated 110 patients with liver metastases (colorectal, breast, gastric, pancreatic, esophageal, melanoma, cholangiocarcinoma, and pharyngeal) unresponsive to systemic chemotherapy and not amenable to local therapy. Approximately 60% received whole-liver SIRT (⁹⁰Y), 20% sequential, and the remainder lobar. Among CRC patients, CR or PR was seen in 46%, while in breast cancer patients CR/PR was 44%. ⁹⁰Y achieved clinically relevant response rates and was well tolerated, indicating a potential therapy for patients with metastatic disease to the liver.⁴⁵

The same Italian group performed a study to evaluate ⁹⁰Y SIRT in 52 patients with metastatic breast cancer. The motivation arose from the fact that only 10% to 20% of patients with hepatic metastases from breast cancer can undergo attempted resection and therefore additional therapies require evaluation. The selected patients were inoperable with chemotherapy-unresponsive hepatic metastases. Patients with less than 25% liver involvement had 54% PR and median survival of 14.3 months, while patients with 26% to 50% liver involvement had 60% PR and median survival of 8.2 months. Considering these patients were receiving salvage therapy, the authors suggested studies investigating earlier use of SIRT (potentially in combination with standard therapies) in metastatic disease to the liver.⁴⁶

In 2012, a group of experts in the management of patients with liver
metastases from NET convened to determine appropriate treatment in patients who are not candidates for surgery or RFA. They examined 18 reports on utilization of transarterial embolization (TAE) and TACE (11 publications), or radioembolization (7 publications). In the studies evaluating $^{90}$Y treatment, there were response rates ranging from 22.5% to 71.4% and median survival ranging from 22 to 70 months, highlighting the heterogeneity of the studies and populations. In a representative study, Memon et al. investigated $^{90}$Y in 40 patients with unresectable liver metastases from NET. Median liver dose was 113 Gy and lung dose 3.81 Gy. Complete or partial response was noted in 64% with stable disease in 32.5% and median OS was 34 months. Symptom control was achieved in 84%. These response rates and median OS were similar to the wide array observed in TAE/TACE. The panel concluded that future studies are required for direct comparison of the intra-arterial therapies, use of intra-arterial therapy versus systemic therapy, and concomitant use of intra-arterial therapy with systemic therapy in order to optimally define the role of $^{90}$Y in NET metastases the liver. Unfortunately, the broad heterogeneity and rarity of this tumor will make future studies difficult to interpret, since it is unlikely an RCT will be performed.

From these studies, it is apparent that $^{90}$Y treatment for liver tumors is a useful adjunct, but its specific capacity remains to be established. Therefore, due to the necessity of additional studies evaluating SIRT in metastatic disease to the liver, investigations have been established that will help clarify its role. For instance, patients with unresectable CRLM will be randomized to FOLFOX ± bevacizumab versus single-session SIRT + FOLFOX ± bevacizumab (SIRFLOX study) to determine effect on progression-free survival (PFS) and OS. The premise of this study (and another similar study, FOXFIRE) is the increased PFS observed in patients with CRLM that received 5-FU/LV and SIRT (18.6 months) versus 5-FU/LV (3.6 months). These, along with additional ongoing studies, will better delineate the optimal patient selection for $^{90}$Y-SIRT, either as monotherapy or in combination with other modalities.

**INDICATIONS**

In general, patients with Eastern Cooperative Oncology Group (ECOG)
performance status of 0 to 2 without extrahepatic life-limiting disease, and adequate hematologic parameters with appropriate pulmonary, renal (creatinine <2 mg/dL), and liver function (bilirubin <2.0 mg/dL) are candidates for SIRT. Multiple malignant tumors (primary and secondary) of the liver have been treated with $^{90}\text{Y}$ radioembolization, allowing for broad application. In addition, patients with disease not amenable to resection or ablation, and who are poor candidates for TACE due to extensive tumor burden or portal vein invasion, or patients who had disease progression following TACE can be treated with SIRT.

When considering transarterial therapy, a noteworthy characteristic of SIRT is the microembolic nature of the $^{90}\text{Y}$-microspheres. Sato et al. evaluated 30 patients undergoing SIRT for unresectable HCC or liver metastases and found that pretreatment arteriography and post-treatment arteriography (1-3 months) revealed 100% patency of first- through third-order vessels and inability of experienced radiologists to correctly determine pre- versus post-treatment imaging based on arterial flow, emphasizing the microembolic character of $^{90}\text{Y}$. In addition, given the microembolic nature of SIRT (as opposed to macroembolic phenomena in TACE), use in patients with portal venous thrombosis has proven safe and effective without the risk of ischemic hepatitis and hepatic decompensation seen with chemoembolization. Furthermore, $^{90}\text{Y}$ radioembolization is equally well tolerated in young patients compared to those greater than age 70, indicating an appropriate treatment option for the elderly patient population whose frailty may limit alternative treatment methods.

Contraindications include excessive estimated radiation doses to the lungs (>30 Gy single dose or >50 Gy multiple doses), uncorrectable flow to the gastrointestinal tract on angiography (ie, inability to occlude aberrant vessels), poor hepatic synthetic function (albumin <3 mg/dL), signs of limited hepatic reserve (bilirubin >3 mg/dL in absence of reversible cause, ascites, encephalopathy, recent variceal hemorrhage), or significant extrahepatic disease that is life-limiting.

**COMPLICATIONS**

Radioembolization-induced liver disease (REILD) is a syndrome manifest from sinusoidal obstruction that occurs 4 to 8 weeks after treatment. Patients developed jaundice, ascites, and moderate increase in canalicular enzymes;
this occurs in 8% to 15% of patients undergoing partial liver radioembolization and is mostly transient but can be severe in approximately 3.1%. Other adverse effects from SIRT include fatigue (50%), nausea or emesis (30%), abdominal pain (20%-30%), fever (10%-15%), pneumonitis (rare), and gastrointestinal ulcers (1%-3%)—the overwhelming majority of which are grade I or II adverse events.

**ABLATION**

Ablative techniques achieve local control of tumor cells with minimal impact to adjacent, healthy liver tissue. In comparison to surgical resection, image-guided local control modalities offer reduced morbidity and mortality. Ablative therapy, either as monotherapy or adjunct to surgical resection, has allowed treatment of bilobar disease as well as treatment of patients who are unsuitable for liver resection due to underlying medical comorbidity. There is a vast array of ablative techniques including percutaneous ethanol injection (PEI), cryoablation, irreversible electroporation (IRE), percutaneous laser ablation (PLA; or LITT), high-intensity focused ultrasound (HIFU), stereotactic body radiation therapy (SBRT), MWA, and RFA. While many of these therapies have been used for local ablation, the most commonly used modality is RFA, with growing enthusiasm for and increasing use of MWA. In addition, SBRT is a noninvasive ablative modality that has generated much interest due to potential applications. Finally, IRE is the newest ablative technique, which offers a unique alternative, and its use has been emphasized in certain patient populations. Therefore, the focus of the ensuing section includes RFA, MWA, SBRT, and IRE.

**Radiofrequency Ablation**

**TECHNIQUE**

Although other ablative methods have become increasingly common, RFA is currently the most frequently used thermoablative technique. First utilized in 1990 for treatment of hepatic tumors, RFA consists of high-frequency oscillating electrical currents (460-500 kHz) delivered from one or more electrodes that produces resistive heating surrounding the electrode(s) (generally 2- or 3-cm exposed tip), ultimately causing tissue hyperthermia.
 (>100°C) and coagulative necrosis (Fig. 59-4). The frictional heat arises from ion movement due to the alternating current, and the localized tissue hyperthermia occurs immediately adjacent to the electrode centered within the tumor. Upon reaching temperatures >60°C, microvascular thrombosis, ischemia, tissue hypoxia, and protein denaturation occur.

**FIGURE 59-4** Radiofrequency ablation (RFA) for hepatic metastasis. (A) RFA electrode tips with approximately 2 to 3 cm of exposed electrode. RFA consists of high-frequency oscillating electrical currents (460-500 kHz).
delivered from one or more electrodes from the exposed portion of the tip, ultimately causing tissue hyperthermia (>100°C) and coagulative necrosis.  

(B) A target hepatic metastasis is demonstrated in segment VI/VII of the liver prior to ablation. (C) Cross-sectional imaging obtained during the ablation procedure demonstrating RFA electrode tips within the lesion.

For percutaneous RFA, patients undergo general anesthesia with placement of grounding pads and ultrasound guidance of electrode insertion into the tumor. In general, the ablation is performed with a total ablative area encompassing the tumor and 0.5 to 1.0 cm margin (Fig. 59-5).
FIGURE 59-5 Radiofrequency ablation (RFA) and follow-up imaging. (A) A metastatic lesion is present in segment VI/VII of the liver, prior to ablation.
(B) Cross-sectional imaging demonstrates an area of coagulative necrosis encompassing the entirety of the hepatic lesion, 3 days post-ablation. (C) Cross-sectional imaging demonstrates the completely ablated lesion 2 months following RFA.

OUTCOMES

There have not been any randomized studies comparing surgical resection with RFA in hepatic CRLM. However, a compilation of studies investigating RFA versus surgical resection for liver metastases demonstrated that surgical resection provided superior OS compared to RFA.54

A retrospective review by Schiffman et al. sought to evaluate the impact on OS of local treatment choice (thermal ablation \([n = 46]\) vs hepatectomy \([n = 94]\)) in solitary CRLM. While disease-free survival (DFS) was not significantly different between the two treatment modalities (42.6 months vs 55.2 months, \(p = .073\)), median OS was substantially different (50.2 months vs 112.7 months, \(p = .005\)), indicating that even for solitary lesions, hepatic resection should be considered first-line treatment.55

McKay and colleagues performed a retrospective study of RFA versus hepatic resection for CRLM. Patients undergoing hepatic resection had increased operative time (269 vs 204 minutes, \(p < .005\)), blood loss (1400 mL vs 150 mL, \(p < .005\)), and transfusion requirements (44% of patients vs 5%, \(p < .005\)). There was no difference in median length of stay (7 days) or complications (59% vs 43%). Multivariate analysis revealed procedure (hepatic resection vs RFA), size of metastasis (>5 cm vs <5 cm), number of lesions (<5 vs 5 or more), and timing of lesion (synchronous vs metachronous) were associated with survival. Patients undergoing hepatic resection had a median OS of 3.8 years versus 2.6 years in patients undergoing RFA, and 5-year OS was 43% versus 23% \((p = .02)\), indicating hepatic resection was superior to RFA. However, these data are immensely flawed by the selection bias that exists in the absence of a randomized controlled trial (RCT), reflected by the fact that patients who underwent RFA were considered poor surgical candidates as a consequence of insufficient projected liver remnant, proximity to critical structures, comorbid conditions precluding resection, or patient refusal of hepatic resection. Therefore, a substantive comparison could not be accomplished, and RFA appeared to be a safe and efficacious modality in these high-risk patients.56
A similar investigation by Kim and colleagues demonstrated comparable outcomes for RFA versus resection in patients with metastatic lesions less than 3 cm. They evaluated 482 patients undergoing RFA (177), hepatic resection (278), or both (27) for synchronous or metachronous CRLM. In this study, RFA was performed for patients with prohibitive comorbidities for surgical resection (cardiovascular or pulmonary disease), for difficult anatomical site, or if there were more than four hepatic metastases. Patients treated by hepatic resection mostly underwent subsegmentectomy/wedge resection \((n = 222)\), segmentectomy \((n = 42)\), or lobectomy \((n = 14)\). Both groups received postoperative chemotherapy (93% RFA vs 89% surgery). In subgroup analysis, 5-year OS was equivalent in hepatic resection and RFA (51.1% vs 51.2%) for solitary liver metastasis less than 3 cm in size. For patients with solitary lesions greater than 3 cm, 5-year DFS was significantly lower in the RFA group (23.1% vs 36.6%, \(p = .01\)). Multiple liver lesions also proved to be associated, with worse 5-year DFS in patients undergoing RFA compared to surgical resection (6.4% vs 16.2%, \(p = .037\)), although 5-year OS was not statistically significantly different (22.9% vs 34.6%, \(p = .330\)). Hospital length of stay was greater for the surgery group (13.4 days vs 4.2 days, \(p < .001\)), and complication rate was significantly higher (21.2% vs 6.2%, \(p < .001\)). In contrast to the previous study which demonstrated high rates of transfusion requirement, bleeding necessitating transfusion occurred in 1% of patients undergoing RFA versus 5% in the resection group (more concordant with expected rates of transfusion requirement). Importantly, in patients with liver metastases less than 3 cm in size (solitary), RFA was not inferior to surgical resection. Furthermore, the authors suggested that despite less robust 5-year DFS in patients with lesions greater than 3 cm or multiple lesions treated with RFA, these results demonstrate that RFA is an effective alternative to surgery, especially in the higher-risk selected population with comorbid conditions or prohibitive location of lesions.\(^{57}\)

Although the heterogeneity in patient populations creates difficulty for direct comparison, the improved DFS and OS establishes surgical resection as the standard, while RFA is an effective and potentially equivalent alternative in appropriately selected patients.

**INDICATIONS**

In addition to RFA for primary liver tumors (HCC), RFA can be utilized for
unresectable metastases to the liver including colorectal and neuroendocrine tumors. In addition, RFA is an accepted alternative to surgical resection in selected patients with contraindication to hepatic resection. Furthermore, RFA can be combined with hepatic resection for curative intent in patients with multisegment or bilobed metastatic liver disease.

While RFA has demonstrated efficacy against tumors <3 cm, with potential application in tumors 3 to 5 cm, there is limited effectiveness in tumors above this size. RFA should be used with caution in tumors with proximity to large vessels (distance <0.5 cm) such as primary or secondary branches of the portal vein, the insertion of hepatic veins, inferior vena cava, or less than 0.5 cm from extrahepatic organs. In addition, a heat dissipation effect as a result of blood flow can be seen near large vessels, such as near the liver hilum, in which proximity to the bile duct and the thermal energy required to produce adequate ablation can result in bile duct injury.

**COMPLICATIONS**

Aside from pain, potential complications following RFA occur in 8% to 35% of patients and include fever, cutaneous burns (up to 8%), viscus perforation, bleeding, abscess formation, and biliary injury; the rate of mortality is approximately 0.5%. Needle track seeding has also been documented, occurring in approximately 0.9% of cases.

**Microwave Ablation**

**TECHNIQUE**

One of the limiting factors of RFA is penetrance through tissues with high impedance such as lung or charred tissue, which occurs with essentially every RFA-treated tumor. As temperatures increase greater than 100°C (adjacent to probes), water vapor formation and tissue dehydration occur, which limits flow of electrical current. For this reason, RFA is temperature controlled such that gradual heating occurs to a maximum temperature not greater than 100°C. In contrast, MWA creates local tissue hyperthermia via an electromagnetic field that causes polar molecules (eg, water) to continuously attempt to align with the oscillating field. The resultant rapidly oscillating molecules produce tissue hyperthermia and can achieve temperatures greater
than 100°C with cell death by coagulation necrosis.\textsuperscript{60} MWA antennas operate at a frequency of 915 MHz or 2.45 GHz and a power between 60 and 100 W for duration of 60 to 300 seconds. MWA fields can overlap in tissue, allowing multiple applicators for larger ablation zone compared to RFA. In addition, given the ability to penetrate through high-impedance tissues with poor electrical conduction such as pulmonary parenchyma and ablated tissue, ablation times are faster than RFA.\textsuperscript{59,61,62} The goal ablation zone encompasses the liver lesion and a 0.5 to 1.0 cm rim of adjacent liver tissue (Fig. 59-6). An additional benefit includes a less pronounced heat-sink effect as is seen in RFA.\textsuperscript{60} Inside the antenna shaft, chilled saline (4°C) or gas (CO\textsubscript{2}) is circulated continuously in order to prevent burn injury at the skin entry site. Following the ablation procedure, contrast-enhanced CT or MRI is obtained (1 month post-treatment) to evaluate for residual tumor. Incomplete ablation is identified as any irregular contrast enhancement within or adjacent to the ablation zone, while complete ablation produces a non-enhancing region encompassing the location of the tumor.\textsuperscript{62}
**FIGURE 59-6** Microwave ablation (MWA) in a patient with metastatic colorectal cancer. (A,B) Cross-sectional imaging demonstrates small 1-cm lesions adjacent to each other in the right lobe of the liver, preablation. (C,D) Intraprocedural ultrasound of MWA of the same colorectal liver metastases. (E) Cross-sectional imaging after the first ablation demonstrates successful ablation of peripheral most lesion. (F) Cross-sectional imaging after second ablation demonstrating successful ablation of more central lesion; the short, thick arrow identifies the first ablation zone and the long, thin arrows reveal the second ablation zone.

**OUTCOMES**

Although MWA is a relatively more recent technology than RFA, it has been studied in both primary liver tumors and metastatic disease and has been found to have equivalent ablation rates, median survival, and OS compared to patients undergoing RFA.\textsuperscript{61-63} In a study investigating 879 patients with liver tumors (HCC \( n = 770 \), metastatic tumors \( n = 85 \), cholangiocarcinoma \( n = 24 \)), the safety profile of RFA \( n = 323 \) was compared to that of MWA \( n = 556 \). Both percutaneous and open ablation was performed and ablation was utilized because of unsuitability for surgical resection or patient refusal.
Based on follow-up imaging obtained at 1 month, complete ablation was achieved in 98.6% after RFA and 99.1% after MWA. Major complications (3.5% vs 3.1%), minor complications (5.9% vs 5.7%), and mortality (0.31% vs 0.36%) were not different between RFA and MWA, indicating MWA has a comparable safety profile.63

Stattnner et al. recently performed a comprehensive review of the literature for microwave ablation of CRLM, and additionally reported their single-institutional experience. The institutional experience included 28 patients undergoing simultaneous MWA and hepatic resection for unresectable CRLM (n = 28). Complications occurred in 39% (6% major complications) and mortality was 0%. Only one recurrence in an ablated tumor occurred and 1-, 3-, and 5-year OS was 82%, 45%, and 18%, respectively, highlighting the importance of MWA as an adjunct to surgical resection. These authors noted that in the literature, a common application of MWA was during concomitant hepatic resection. However, they also reviewed the comparison to RFA and identified potential advantages such as decreased local recurrence (LR).64 For instance, Martin et al. compared MWA to a matched RFA group and complete ablation rate was higher in patients receiving MWA versus RFA (98% vs 92%) with shorter ablation times (13 min vs 40 min) and operative times (57 min vs 126 min). LR was 6% in patients undergoing MWA versus 17% in those undergoing RFA.65

Stattnner and colleagues proposed that in the setting of CRLM, MWA is a safe and efficacious modality with reduced local recurrence compared to RFA. This was thought to be secondary to lack of a heat-sink effect such that lesions adjacent to large vessels received complete ablation; additionally, they noted that the desiccation and impedance that limit effectiveness of RFA in lesions >3 cm does not occur with MWA. Although similar 1-year and 3-year survival were seen in patients undergoing MWA versus hepatectomy for CRLM (71% and 14% vs 69% and 23%),66 the authors concluded that MWA should be used concomitantly with surgery or instead of surgery when surgical resection is not feasible (tumor size, location, bilobar disease, number of lesions, or patient comorbid conditions). In addition, studies focusing on comparison of MWA versus RFA as well as MWA versus surgical resection would clarify the role of MWA in liver tumors.64

INDICATIONS
Considering the efficacy of MWA with shorter ablation times compared to RFA, MWA is increasingly being employed for primary liver tumors and hepatic metastases. Many of the indications are similar to those of RFA with the potential benefit of lesion ablation near vascular structures. MWA can be used when surgical resection is not suitable due to tumor (ie, location, distribution, or number) or patient characteristics. In addition, MWA should also be considered an adjunct to surgery and can potentially transform a two-stage resection into a single resection with ablation.\textsuperscript{64}

**COMPLICATIONS**

Although grounding pads are not used, burn complications can occur along the microwave applicator shaft (entry site), which should be alleviated by the cooling system of the shaft. Post-procedural pain is a fairly common occurrence (60%), as is fever (80%) and asymptomatic pleural effusion (10%-15%). Major complications occur in approximately 2% to 4% and include hemothorax, diaphragmatic hernia, liver decompensation, intrahepatic hematoma, liver abscess, bile leak, biloma, bile duct injury, portal vein thrombosis, and peritoneal hemorrhage. Mortality (30-day) after MWA in the larger series is approximately 0.3% to 0.4.\textsuperscript{63}

**Stereotactic Body Radiation Therapy**

Historically, radiotherapy has not been utilized for liver tumors due to the radiosensitivity of liver tissue; doses sufficient to achieve tumor cell death would result in unacceptable toxicity and collateral cell damage.\textsuperscript{67} Whole-liver radiation can result in radiation-induced liver disease (RILD) in up to 50% at doses of 36 Gy in 2-Gy fractions.\textsuperscript{68} RILD is characterized by ascites accompanied by elevation of alkaline phosphatase and transaminases, and can potentially result in liver failure and mortality.\textsuperscript{69} However, with the advent of highly conformal dosimetry and steep dose gradient seen with SBRT, tumor targeting can be achieved with relative sparing of the adjacent normal tissue. SBRT developed from intracranial single-fraction stereotactic radiotherapy and is generally performed in five or fewer fractions with doses up to 30 Gy when delivering a single fraction and doses up to 75 Gy over multiple fractions.\textsuperscript{70} In contrast to conventional external beam radiation
therapy, which delivers fractions ranging from 1.5 to 3.0 Gy to a larger treatment volume, SBRT delivers doses ranging from 30 to 75 Gy in 1 to 5 fractions to achieve local control. In addition, although toxicity of SBRT with concurrent chemotherapy has not been well studied, chemotherapy should be stopped 2 weeks prior to planned treatment and can be resumed 2 weeks following completion of treatment, with the exception of clinical trial or endocrine therapy.

Many of the alternative therapies for locoregional control such as RFA, MWA, cryotherapy, IRE, TACE, and SIRT require some level of invasiveness and are accompanied by certain restrictions. In patients who are not candidates for surgical extirpation, SBRT may be preferable over transarterial (SIRT or TACE) and ablative therapies (RFA or MWA) in patients who have poor blood flow or centrally located tumors and in those with peripherally located lesions or tumors adjacent to major vessels. Therefore, SBRT is a noninvasive additional therapeutic option that can be utilized to treat liver metastases in selective patient populations; the noninvasive aspect allows for delivery on an outpatient basis.

**TECHNIQUE**

The safe delivery of high-dose radiation therapy to specific locations mandates effective patient immobilization combined with precise targeting and steep isodose gradient outside the projected treatment volume. In contrast to treatment of brain lesions, extracranial tumor sites move between and during each delivered fraction of radiotherapy. Therefore, subsequent to patient evaluation and multidisciplinary discussion, SBRT requires significant preparation to optimize control of liver tumors. Patients often undergo multimodal imaging including three-phase contrast-enhanced CT, which is accompanied by MRI and/or PET/CT to improve target definition. Four-dimensional CT scan is also acquired in order to delineate organ movement during respiration. The clinical target volume (CTV) equates to the gross tumor volume (GTV) and internal target volume (ITV) is comprised of GTV throughout the respiratory phases; planned target volume (PTV) encompasses ITV with an additional 5-mm margin. Through the use of respiratory techniques (eg, controlled breath holds or shallow breathing) and abdominal compression devices (eg, corsets or plates) to limit abdominal movement, displacement of tumor during respiration can be minimized. In
addition, the patient may undergo placement of radiopaque fiducial markers within the lesion to assist in image guidance. An ablative dose prescription is then determined with multiple beams using coplanar and non-coplanar geometries; the nominal doses prescribed are a reflection of the isodose lines that encompass the ITV with steep dose gradients as distance from tumor increases. Since a dose-response for local control appears evident, a total prescription of 48 Gy or higher in 3 fractions is recommended. In addition, constraints for organs at risk apply: greater than 700 mL of liver volume should receive <15 Gy, a maximum volume of 0.1 cm$^3$ of spinal cord receive <18 Gy, a maximum of 35% of the kidneys receive <15 Gy, a maximum of 5 cm$^3$ of duodenum, small bowel, esophagus, and stomach receive <21 Gy and a maximum of 5 cm$^3$ of the heart receives <30 Gy. The radiotherapy systems most commonly utilized are linear accelerators (linacs) with on-board imaging capabilities to deliver image-guided SBRT.

Response is determined by follow-up imaging and can pose a challenge due to radiation-induced changes in tumor and surrounding liver tissue. Patterns of contrast enhancement, changes in hypodensity, and displacement of vessels seen on CT or MRI indicate local control.

OUTCOMES

Expected local control rates vary from 70% to 100% at 1 year and 60% to 90% at 2 years depending on tumor volume, prior therapy, and dose delivered. Median OS after SBRT is on the order of 10 to 34 months, with the majority of patients experiencing metastatic spread outside the treatment field; thus, SBRT is often combined with systemic treatment in order to achieve improved OS.

In a single-institution experience of SBRT for 74 patients ineligible for surgery (local tumor extension or patient comorbidities) and lesions not amenable to other local or systemic therapy, median local recurrence-free interval was 23 months, with 75% local control rate at 1 year; median OS was 27 months. Previous treatments had included systemic chemotherapy, resection, or other local ablative procedures, and primary sites consisted of mostly colon cancer ($n = 37$) and breast cancer ($n = 12$), with the remainder comprised of esophageal, stomach, pancreas, biliary, and other ($n = 25$). Median dose was 35 Gy over 5 fractions and median tumor volume was 45
A pooled analysis of SBRT in CRLM performed by Chang et al. identified 65 patients with one to four unresectable liver lesions who underwent a median dose of 41.7 Gy over 6 fractions. The majority of patients had received pretreatment chemotherapy (73%). The 12-month and 24-month OS was 72% and 38% with nearly 70% of patients experiencing progression outside the liver; the in-field local recurrence was 29% at 16-month follow-up. The authors found that 12-month and 24-month local control was 84% and 66%, respectively, for patients receiving >42 Gy versus 48% and 43%, respectively, for patients receiving <42 Gy. From the data, the authors used tumor control probability curves and suggested that 12-month local control could be achieved in 90% if delivering 46 to 52 Gy in 3 fractions; total dose, dose per fraction, and biologically effective dose correlated with local control.

In congruence with the suggested dose of 46 to 52 Gy, a multi-institutional phase I/II study evaluated patients with one to three liver metastases (CRC and non-CRC) less than 6 cm in size and appropriate underlying liver function who underwent SBRT. Chemotherapy (in 41/47 patients) was stopped at least 14 days prior to radiation therapy and low-burden, potentially treatable extrahepatic disease was present in 21/47 patients. The phase I aspect of the study identified no toxicity when escalating from 36 Gy to 60 Gy, and the phase II study evaluated 47 patients receiving 60 Gy in 3 fractions. The majority of patients had a single lesion (28/47) while the remaining had two (7/47) or three (12/47) lesions; local control was 95% and 92% at 1 and 2 years, respectively. Lesions less than 3 cm (60% of lesions) had 2-year control of 100% versus 77% for lesions greater than 3 cm (40% of lesions). Despite the achieved local control, distant progression (distant intrahepatic and extrahepatic) occurred in 83% of patients at a median of 6 months. Median and 2-yr OS was 20.5 months and 30%, respectively, and primary tumor site was predictive of survival; lung, ovarian, and noncolorectal gastrointestinal malignancies had median OS of 12 months versus breast, colorectal, renal, carcinoid, GIST, and sarcoma, which had 32-month median OS (p < 0.001). The SBRT was well tolerated, with one instance of grade III soft tissue toxicity. These authors emphasized the importance of higher dose and low fraction number for achieving adequate local control.

A more recent study by Scorsetti and colleagues evaluated 61 patients
with liver metastases (colorectal \[n = 29\], breast \[n = 11\], gynecologic \[n = 7\], melanoma/pancreatic/RCC/biliary \[n = 14\]) who were not suitable for surgery, with tumor diameter less than 6 cm and number less than 3 lesions; additionally, there was no evidence of progressive disease or untreated disease outside the liver. Prescription dose was 75 Gy in 3 fractions, although this was not possible in 18\% of patients due to organs at risk (received 52.5-67.5 Gy). Local control rates were 90.6\% at 2 years with no difference between patients with lesions <3 cm versus >3 cm. These authors concluded that at higher doses, effective treatment can be accomplished in lesions 3 to 6 cm in size, which provides an advantage for local control over many other ablative techniques.  

Although there are numerous additional retrospective and prospective analyses of SBRT in liver metastases, there is significant heterogeneity in primary tumor sites, extent of extrahepatic disease burden, prior treatments received, and dose/fractions of SBRT. Furthermore, there is a paucity of investigations comparing SBRT to alternative modalities. Currently, there is a multicenter randomized phase III trial evaluating patients with one to four inoperable colorectal liver metastases no larger than 4 cm in size who are randomized to RFA or SBRT (The International Liver Tumor Group RAS-Trial Radiofrequency Ablation versus Stereotactic Body Radiation Therapy for Colorectal Liver Metastases: A Randomized Trial [RAS01 Clinical Trials.gov, available at https://clinicaltrials.gov/ct2/show/NCT01233544?term=ras01&rank=1]). The primary endpoint is local PFS, and this trial should provide additional information regarding the therapeutic role of SBRT in liver metastases. Currently, SBRT appears to be a safe and effective modality for local control, even to lesions of 6 cm in size.

**INDICATIONS**

Similar to other modalities used to treat liver metastases, the determination of SBRT treatment of liver tumors should be made in a multidisciplinary tumor board discussion. Patients suitable for treatment include those with four or fewer lesions, diameter up to 6 cm (advantage of this modality over RFA and MWA), and greater than 8 mm from organs at risk. Patients generally have a good performance status with absent or stable extrahepatic disease as well as healthy underlying liver function (total bilirubin <1.5 × upper limit normal, albumin >3 g/dL, transaminases <1.5 × upper limit normal, normal INR) and
adequate hepatic volume. Those with five or more lesions, lesions greater than 6 cm diameter, poor underlying liver function (Child C), insufficient liver volume, or tumor location less than 5 mm from organs at risk are not candidates for SBRT. SBRT has been utilized for numerous primary tumors metastatic to the liver including colorectal, breast, carcinoid, lung, melanoma, gallbladder, ovarian, esophageal, and pancreatic cancer. While OS varies between the primary sites, effective local control has been demonstrated irrespective of malignant primary. In general, smaller tumor volumes are associated with improved local control; additional positive prognostic factors include higher delivered dose, longer disease-free interval, absence of chemotherapy, and adenocarcinoma histology.

**COMPLICATIONS**

Most series report Common Terminology Criteria for Adverse Events (CTCAE) grade III or IV toxicity complicating approximately 1% to 10% of liver SBRT. Tumor size and treatment dose are important considerations in order to avoid RILD, which is a result of injury to surrounding healthy liver parenchyma when radiating the hepatic metastases. This complication more commonly occurs in patients with HCC due to the diffusely dysfunctional state of liver parenchyma. In the setting of liver metastases, RILD is rare (<1%), although most series reporting complications have performed SBRT on single metastases. In addition, it has been shown that grade II or higher hepatobiliary toxicity can be avoided when at least 700 mL of liver volume receives less than 21 Gy; therefore, to avoid hepatobiliary toxicity, mean recommended liver radiation dose is 15 Gy with at least 700 mL of liver receiving less than 15 Gy over 3 to 5 fractions.

Other known complications include duodenal ulceration and intestinal perforation; for this reason, ideal locations of SBRT-treated lesions are greater than 8 mm away from visceral organs at risk. In addition, soft tissue toxicity and nontraumatic rib fractures can occur for lesions close to subcutaneous tissue and ribs. Grade I to II toxicity can include fatigue (up to 20%), nausea/vomiting (15%-20%), fever (5%-10%), abdominal pain (5%-10%), skin reaction (5%), and pneumonitis (1%-2%).

Irreversible Electroporation
Electroporation is characterized by increasing cell permeability achieved through the application of electrical fields across cells, with consequent cell membrane defects that are either temporary (reversible electroporation) or permanent (irreversible electroporation). Reversible electroporation has been utilized extensively as a method to introduce genetic material into cells in vitro. By employing larger electrical fields for longer duration, the cell membrane pores do not reseal and thus the process becomes irreversible, ultimately resulting in disruption of cell homeostasis and cell death. Early studies in animal models focusing on liver ablation identified a well-demarcated nonthermal ablation zone (very narrow transition) confined between the electroporation electrodes; this zone consisted of discriminate cell death and sinusoidal blood vessel congestion while larger vascular structures and bile ducts remained intact. When considering IRE protocols, multiple parameters may be manipulated to achieve optimal cell death including pulse shape, duration, number, polarity, electrode configuration, and geometry. In addition, although IRE was first described for patients with prostate cancer, subsequent studies have evaluated its efficacy in pancreatic cancer, renal cell carcinoma, lung malignancies, and hepatic malignancies.

**TECHNIQUE**

Meticulous treatment planning is an essential aspect for delivery of successful IRE therapy. Factors such as electrode position and number, electric field amplitude, and pulse duration, number, and frequency are evaluated for nonthermal ablation of target tissue. Treatment planning is based upon preoperative imaging (CT) to determine tumor dimensions and morphology. This will allow calculation of number and spacing of probes. IRE image guidance (US, CT, and MRI) can be used for electrode positioning as well as to monitor the ablation procedure and the ablation zone. In the liver, the ablated region is sharply demarcated on imaging which has excellent correlation to the histologic actual ablation zone (initially hypoechoic on ultrasound with transition to hyperechoic in 24 hours; hypodensitizing core with hyperdensitizing rim on CT at 48 hours).

Patients undergo general anesthesia with deep sedation and complete muscle relaxation; additionally, monitors and synchronization devices are
used in order to synchronize the pulse delivery with simultaneous electrocardiography. Delivery of the pulses from the IRE device occur during the refractory period (approximately 50 msec after R-wave) to avoid arrhythmia genesis. Image guidance is generally achieved with CT guidance or ultrasound, either transabdominal if performing percutaneous ablation or intraoperative ultrasound when performing laparoscopic or open ablation. The radiopaque insulated needle electrodes (20 mm exposure length) are 15 cm or 25 cm in length and are placed around the periphery of the tumor in parallel configuration (they must be placed within 10° of parallel to avoid treatment failure) with approximately 20 mm distance between each electrode. Pulsatile electric fields (1000-3000 V/cm) with variable pulse number (typically 90-100) and duration (approximately 20-100 msec) are applied; these parameters are determined by a standard algorithm incorporating factors such as size of ablation zone, number of probes, and distance between probes. For larger tumors, the electrodes are pulled back 1.5 cm to continue ablation of the superficial component after ablating the deep aspect of the tumor, and an additional margin of 1 cm around the tumor is generally included.

Follow-up imaging is obtained within 2 weeks in order to evaluate for changes associated with treatment as well as potential complications such as portal vein thrombosis. Subsequently, cross-sectional imaging is obtained at 3-month intervals.

**OUTCOMES**

The COLDFIRE-1 ablate-and-resect study evaluated ten patients with at least one resectable CRLM smaller than 3.5 cm who underwent open IRE followed by resection of the treated lesion. Patients were excluded if they had cardiac arrhythmias, pacemaker in place, epilepsy, or previous treatment of the lesion(s). At least 1 hour after IRE, the lesion was resected and evaluated. Median lesion size was 2.4 cm and mean ablation time was 25 minutes with IRE delivery time of 182 seconds. One IRE-related adverse event occurred (ventricular extrasystole), which resolved without issue. Histologic evaluation revealed a well-demarcated ablation zone encompassing tumor with preservation of traversing larger portal and arterial and venous vasculature as well as bile ducts. Complete ablation occurred in 9/10 tumors and ultrasound correlated well with ablation margin.
Eisele and colleagues reported the feasibility and success of ultrasound-guided IRE in 13 patients with 14 unresectable liver tumors (colorectal liver metastases \( n = 6 \), HCC \( n = 5 \) or cholangiocarcinoma \( n = 2 \)) and small centrally located tumors. IRE was performed instead of RFA or MWA in cases of tumor proximity to major vessels (portal or hepatic veins; average tumor size 1.5 cm). Seven patients underwent percutaneous ablation, four patients had laparoscopic ablation, and two patients had concomitant open ablation with hepatic resection. There were no treatment-related complications, and local recurrence related to incomplete ablation occurred in 3/14 tumors (all failures in percutaneous) at a median of 6 months follow-up. The authors commented on the difficult location of tumors (adjacent to major vessels), which provided hesitancy to employ MWA or RFA and therefore IRE was advantageous. They suggested adjunct cross-sectional imaging for needle placement to avoid failures during percutaneous IRE ablation.88

Kingham et al. retrospectively evaluated 28 patients undergoing IRE to treat 65 tumors (CRLM 75\%, HCC 7\%, NET 7\%, other 11\%) in which the majority were located within 1 cm of a major hepatic vein or major portal pedicle. Median tumor size was 1 cm and percutaneous approach was used in 6/28 patients while laparotomy was used in 22/28 patients. There were three local recurrences and one persistent tumor for a consequent 7.5\% local failure rate. The authors concluded that the low treatment failure rate given the tumor location was encouraging.90

One of the larger series on IRE was performed by Cannon and colleagues. Forty-four patients underwent 48 IRE procedures for centrally located tumors (CRLM \( n = 20 \), HCC \( n = 14 \), non-small cell lung carcinoma (NSCLC) \( n = 2 \), breast \( n = 2 \), NET \( n = 3 \), other \( n = 3 \)) adjacent to major vascular or biliary structures or nearby organs. Percutaneous approach was used in 63\% with laparoscopic in 5\% and laparotomy in 32\%; complete ablation was achieved in 100\% of patients. A total of nine adverse events occurred but no treatment-related deaths or biliary stricture/portal vein thrombosis. Local recurrence-free survival was 94.6\% and 59.5\% at 6 months and 12 months, respectively, while local recurrence-free survival for lesions <3 cm was 100\% and 98\% at 6 months and 12 months, respectively. Although 72\% of patients had received prior treatment (chemotherapy in 60\%, liver-directed therapy in 55\%), IRE was quite effective for lesions less than 3 cm. The authors concluded that IRE appears best suited for salvage therapy or for tumor location precluding alternative therapies in tumors <3 to 4 cm in diameter.
With accumulating experience, factors such as patient selection, technique (probe number and placement), and image guidance improvement will allow further delineation of the role of IRE.  

**INDICATIONS**

One of the putative benefits of IRE is the ability to produce tissue ablation even in proximity of large vessels (or traversing the ablation zone) without a heat-sink effect.\(^8^5\) IRE-ablation of liver tissue adjacent to structures such as hepatic arteries, hepatic veins, portal veins, and intrahepatic bile ducts results in preservation of these critical structures.\(^8^4,^8^6\) Therefore, IRE can be utilized for local ablation of unresectable tumors adjacent to major vascular or biliary structures and has even been used as an adjunct to facilitate extended resection (margin ablation) when location adjacent to vasculature precludes R0 resection.\(^9^1\) However, IRE has only recently been utilized (since 2007) for treatment of malignant disease, and therefore specific indications remain in evolution.

**COMPLICATIONS**

IRE requires general anesthesia with paralysis due to prominent muscle contraction from the electrical field. In addition, IRE can produce cardiac arrhythmias, and therefore patients with structural or functional cardiac disease would be highly susceptible; this can be offset by utilization of a cardiac synchronization device such that IRE can only be performed during the non-vulnerable period of the cardiac cycle.\(^8^4\) Incomplete ablation can arise in the setting of difficult electrode placement. The distance between the electrodes must remain precise and the parallel configuration must also be maintained in order to accomplish the projected ablation zone.\(^8^8\) Additional considerations include abdominal pain, hemorrhage, hematoma, and infection.\(^9^0\)

**CONCLUSIONS**

Treatment of hepatic tumors and metastatic liver disease has evolved significantly due to the various therapeutic options currently available. While
resection (or transplantation) is generally considered the standard, there are many tumor features and patient characteristics that prohibit these options. Therefore, in the setting of local disease, RFA, MWA, and SBRT can achieve local control, with potential applications for IRE. With locoregional disease, transarterial-directed therapy including chemoembolization and radioembolization have gained recognition as treatment options even in patients with severe comorbidities or advanced stage disease. Although investigations are attempting to better delineate the role of each of these modalities in primary and secondary liver tumors, the variability in patient and tumor characteristics highlights the necessity for careful patient and treatment selection in a multidisciplinary setting.

ACKNOWLEDGMENTS

Dr. Jason Pinchot at University of Wisconsin Hospital and Clinics department of interventional radiology for providing images related to TACE and SIRT.

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INTRODUCTION

Liver resection for benign and malignant conditions has evolved significantly over the past 2 decades. Moreover, considerable interest in the field of liver surgery has led to an increase in the number of surgeons subspecializing in hepatobiliary surgery. This interest has brought significant innovation and evolution to the field including new technologies in minimally invasive approaches, expanded indications for patients with liver metastases, and the ability to plan and perform more complex resections. At the same time, improvements in patient selection, liver function assessment, and perioperative care have significantly improved the safety of liver resection at experienced tertiary centers. The concepts and principles of liver surgery are expertly reviewed in Chapters 56 (Hepatic Abscess and Cystic Disease of the Liver) and 57 (Benign Liver Neoplasms). Herein, we provide a perspective on recent advances in the field of liver resection, their impact on patient outcomes, and where future developments are anticipated.
Indications for Resection

Although the majority of liver resections today are performed for malignant indications, hepatobiliary surgeons should be familiar with the management of benign conditions as well (Table 60-1). Benign simple cysts can typically be characterized with cross-sectional imaging and do not require resection unless they are symptomatic (unusual unless >10 cm) or contain features worrisome for biliary cystadenoma or cystadenocarcinoma. In the former (simple cyst), laparoscopic fenestration is the preferred treatment, whereas in the latter, formal resection or enucleation should be performed. One notable and frequent cause of liver cystic disease globally is echinococcal or hydatid cyst. Surgical resection of the cyst-bearing area of the liver or operative drainage of the cyst (to ensure prevention of spillage and potential anaphylactic shock) is occasionally required. Despite improvements in antimicrobial therapy and percutaneous aspiration and drainage techniques, the need for occasional surgical management of nonechinococcal hepatic abscesses remains. Finally, hepatic adenomas are benign tumors of the liver that have a low rate of malignant transformation and risk of rupture that increases with size, pregnancy, and location of the tumor. Most authors therefore recommend resection of lesions >5 cm or in women of childbearing age with tumors at risk for rupture. Hemangiomas and focal nodular hyperplasias are benign conditions that do not require resection (or surveillance) unless they are symptomatic, which, in general, is rare.
However, the vast majority of liver resections performed by experienced hepatobiliary surgeons are for malignant indications. Although hepatocellular carcinoma (HCC) is one of the most common solid tumors worldwide, only a minority of patients are candidates for resection because of either poor underlying liver function or advanced disease (eg, multifocality, extrahepatic disease, macrovascular invasion). Unlike HCC, cholangiocarcinoma more commonly develops in patients with normal liver function. Resection of cholangiocarcinomas often requires extended resections with or without biliary reconstruction but is nevertheless recommended in patients with adequate liver function and absence of metastatic disease. Similarly, most liver metastases occur in patients with normal liver function, and colorectal liver metastases (CRLM) are now the most common indication for liver resection among Western hepatobiliary surgeons. Largely based on nonrandomized prospective and retrospective data, liver resection for CRLM when feasible has become largely accepted as standard of care given its association with improved survival rates. Other liver metastases from various histologies, for example, neuroendocrine liver metastases, are also regularly considered for surgical resection.

**Patient Selection**

Although advances in perioperative anesthesia, minimally invasive surgery, parenchymal transection techniques, and enhanced recovery protocols have been instrumental, patient selection is paramount to optimizing postoperative outcomes following liver resection. In general, patient selection for liver surgery should be conducted along 3 domains: physiologic, oncologic, and

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Pyogenic abscess</td>
</tr>
<tr>
<td></td>
<td>Echinococcal abscess</td>
</tr>
<tr>
<td></td>
<td>Parasitic abscess</td>
</tr>
<tr>
<td></td>
<td>Chronic hepatolithiasis</td>
</tr>
<tr>
<td>Benign</td>
<td>Simple cyst,^a^ biliary cystadenoma</td>
</tr>
<tr>
<td>Trauma</td>
<td>Strictures/fistulae, choledochal cyst</td>
</tr>
<tr>
<td></td>
<td>Focal nodular hyperplasia,^b^ hemangioma,^a^ hepatic adenoma</td>
</tr>
<tr>
<td>Malignant-primary</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Epithelioid hemangioendothelioma</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>Biliary cystadenocarcinoma</td>
</tr>
<tr>
<td>Malignant-secondary</td>
<td>Colorectal liver metastases</td>
</tr>
<tr>
<td>Colorectal liver metastases</td>
<td>Other liver metastases (eg, breast, sarcoma, genitourinary, gastrointestinal)</td>
</tr>
<tr>
<td>Neuroendocrine liver metastases</td>
<td>Tumors directly invading liver (eg, adrenal, retroperitoneal sarcoma)</td>
</tr>
</tbody>
</table>

^aSymptomatic only.
technical. Physiologic resectability refers to the patient’s capacity to safely tolerate major abdominal surgery. Multiple risk calculators, frailty indices, and other measures have recently been developed to identify patients at highest risk for major complications.\textsuperscript{1,2} Next, oncologic resectability refers to the indications for resection based on the underlying tumor biology. Consideration should be given to the presence of extrahepatic disease, the histopathologic features, disease-free interval (for liver metastases), response to previous therapies (if applicable), and, increasingly, the molecular features of the tumor. Finally, technical resectability should be evaluated based on high-quality cross-sectional imaging. In general, resectability requires retention of 2 contiguous liver segments with adequate vascular inflow, outflow, and biliary drainage as well as sufficient future liver remnant (FLR) volume and function to prevent postoperative hepatic insufficiency (PHI).

Accurate preoperative assessment of the FLR has been one of the most important advances over the past 2 decades, leading to improved risk stratification as well as prevention of PHI and postoperative mortality. Since FLR volume correlates with function and the risk of PHI, a systematic analysis of liver volumetry is imperative in patients undergoing extended hepatectomies or those with compromised liver function. Previous studies have identified FLR size thresholds at which the risk of PHI is prohibitively high: <20\% in chemotherapy-naive patients, <30\% in chemotherapy-treated patients, and <40\% to 50\% in patients with cirrhosis.\textsuperscript{3} In addition to volumetry, several modalities now aim to directly estimate liver function. For example, since indocyanine green (ICG) is exclusively cleared by the liver, the ICG clearance test is useful because the retention rate at 15 minutes has been correlated with postoperative mortality.\textsuperscript{4} In addition, \textsuperscript{99m}Tc-galactosyl human serum albumin (GSA) scintigraphy, which uses an analogue ligand of asialoglycoprotein that binds to asialoglycoprotein receptors on the hepatocyte cell membrane, has recently been introduced as a more sensitive indicator of liver function and, when combined with single-photon emission computed tomography (SPECT)/computed tomography (CT), can directly estimate function of the FLR.\textsuperscript{5}

**EXPANDING INDICATIONS FOR LIVER RESECTION**
FLR Augmentation

Limiting liver resection to patients with adequate FLR volume and function is essential to minimizing postoperative morbidity and mortality. Nevertheless, for patients with inadequate FLR by volumetric analysis, advances in FLR augmentation strategies have expanded the proportion of patients eligible for complex liver resection. Portal vein embolization (PVE) diverts portal blood flow and its inherent growth factors preferentially to the FLR, resulting in 30% to 40% hypertrophic response in most patients. PVE is most frequently used among patients undergoing extended right hepatectomy or as part of a 2-stage hepatectomy (TSH) strategy. While various techniques have been described, PVE should be performed in a transhepatic, ipsilateral fashion using microsphere particles and can be extended to segment IV when extended hemihepatectomy is planned. Among patients who do not achieve an adequate degree of hypertrophy (DH), hepatic vein embolization has been described as a method of promoting additional hypertrophy.

TSH allows for the resection of bilobar CRLM that would otherwise be unresectable using a single-stage technique. In the first stage, the FLR (typically the left lateral section) is cleared of metastatic disease. One to 4 weeks after surgery, a right PVE is performed, which leads to hypertrophy of the FLR. In patients who demonstrate adequate hypertrophy on CT volumetry 3 to 4 weeks after PVE, as well as absence of disease progression, a second-stage operation (typically right or extended right hepatectomy) is performed. TSH with PVE has consistently demonstrated high completion rates, low perioperative morbidity and mortality rates, and excellent overall survival outcomes in experienced centers.

The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure has been introduced as an alternative to traditional TSH. In the first stage of ALPPS, right portal vein ligation is combined with parenchymal transection and clearance of the FLR of metastatic disease. The second stage is performed during the same hospital admission 1 to 2 weeks after the first stage and involves completion hemihepatectomy. Although ALPPS results in rapid FLR hypertrophy and higher completion rates compared to traditional TSH, concerns remain over the relatively high postoperative morbidity and mortality as well as uncertain long-term oncologic outcomes.
It is also important to recognize that the liver’s response to PVE provides an estimation of the FLR’s regenerative capacity. For example, patients who experience an absolute DH of <5% have significantly elevated risks of PHI and postoperative mortality.\textsuperscript{13} In addition, a kinetic growth rate (KGR), measured as the DH divided by the number of weeks since PVE, less than 2% is one of the strongest predictors of PHI.\textsuperscript{14} Using a traditional TSH approach, the response of the liver to PVE can be measured and second-stage surgery (and its inherent morbidity) avoided in patients with inadequate FLR and/or demonstrated regenerative capacity. Given the high rates of PHI and postoperative mortality following second-stage ALPPS, mostly among patients with an FLR >30%, better predictors of PHI are urgently needed. Recent evidence suggests that KGR\textsuperscript{15} and hepatobiliary scintigraphy with SPECT/CT\textsuperscript{16} can accurately identify patients at higher risk for PHI following second-stage ALPPS.

**Repeat Hepatectomy**

As systemic therapies improve and survival durations increase, the proportion of patients who develop hepatic recurrence will only increase. This is especially true among patients with CRLM in whom the recurrence rate following liver resection approaches 50%. However, multiple retrospective series have demonstrated the feasibility, safety, and oncologic outcomes of patients undergoing repeat hepatectomy.\textsuperscript{17} In general, similar outcomes can be expected in these situations as long as a similar approach to patient selection, optimization, and resection techniques is employed. A trend in recent years has been an emphasis on parenchymal sparing approaches—that is, performing nonanatomic resections or minor anatomic resections (eg, segmentectomy, bisegmentectomy) rather than hemihepatectomies. Indeed, parenchymal sparing hepatectomy allows for the opportunity for repeat hepatectomy in the case of future liver recurrence without compromising margin-negative rates or oncologic outcomes compared to traditional approaches.\textsuperscript{18}

**ADVANCES IN RESSECTIONAL TECHNIQUES**
Definitions and Terminology

Advances in hepatobiliary techniques have permitted complex liver resections to be performed at experienced centers while minimizing the risk of perioperative complications. Much of this advancement can be attributed to an improved understanding of segmental liver anatomy. Couinaud\textsuperscript{19} originally described the 8 segments of the liver, each with its own segmental portal pedicle, separated into 4 sectors based on 3 portal scissura marked along the path of the hepatic veins (Fig. 60-1). Since the left hepatic vein divides segments II and III, this partitions the left liver into a left paramedian sector (IV, III) and left lateral sector (II). The Brisbane terminology reclassified the liver into more surgically relevant sections,\textsuperscript{20} which is important given that en bloc resection of segments IV and III cannot be technically performed while leaving segment II in situ. In this description, the left medial section (IVa and IVb) is distinct from the left lateral section (segment II and III), whereas the right liver sectors and sections are concordant. This standardized classification informs the terminology used today to describe common partial liver resections (Table 60-2).

\textbf{FIGURE 60-1} The functional division of the liver and the segments according to Couinaud’s nomenclature.
Additional confusion occasionally ensues regarding the terminology used in classifying major and minor resections. By definition, major resections include ≥3 segments, whereas minor resections involve <3 segments. This designation does not imply complexity, however, as most would argue that a left hepatectomy (major) is technically less demanding than a right posterior sectorectomy (minor). The term parenchymal-sparing hepatectomy (PSH) refers to the concept of preserving noninvolved liver tissue. Whereas the term wedge resection connotes a nonanatomic minor resection, the term PSH does not imply whether the resection was anatomically based or not.

**Surgical Technique**

With this knowledge and consistent with an emphasis on parenchymal-sparing techniques, most minor anatomic resections can be performed with early ultrasound-guided control of the intraparenchymal segmental pedicle.
(eg, Glissonian method). This maneuver allows for parenchymal transection along the line of demarcation, as is typically done for major hepatectomy following extrahepatic inflow division. Alternatively, the segmental pedicle(s) can be injected with dye (eg, ICG or blue dye) for counterstaining followed by parenchymal transection and division of the portal pedicle(s). Regardless of methods, parenchymal-sparing anatomic resections result in less blood loss compared to nonanatomic wedge resections and may be associated with reduced recurrence rates in HCC and CRLM.

Randomized controlled trials have suggested no difference between methods of parenchymal transection, which, in general, should be determined by the expertise of the surgeon. While some prefer a traditional crush-clamp technique, it is the authors’ preference to use a “2-surgeon” technique where the surgeon dissects using the Cavitron Ultrasonic Surgical Aspirator and an assistant provides exposure and divides vessels. In general, small vessels <3 mm can be divided using electrocautery, medium vessels are controlled with titanium clips, and larger vessels >5 mm are divided between suture (Fig. 60-2). Caution should be given to overuse of linear staplers for parenchymal transection because, although simple and efficient, the technique is relatively “blind” and may lead to inadvertent biliary or vascular injury.
FIGURE 60-2 The technique for vascular control during parenchymal transection is based on vessel size. **A.** Vessels less than 3 mm are coagulated and divided using saline-linked cautery. **B.** Vessels from 3 to 5 mm are controlled with titanium clips and sharply divided. **C.** Vascular structures
larger than 5 mm are controlled with 3-0 silk ties and sharply divided.

Controversy continues regarding the role of perioperative drains following liver resection. In general, the routine use of surgical drains following liver resection is not warranted and may be associated with increased complications. Awareness of risk factors for biliary fistula (eg, biliary anastomosis, major liver resection, increased blood loss) may allow for more selective use of drains. It should be noted, however, that in randomized controlled trials, the use of a surgical drain does not decrease the need for subsequent percutaneous drainage. One recent advance in the prevention of postoperative biliary fistula is the performance of an air leak test following parenchymal transection. With the resection surface immersed under water and the surgeon’s hand manually compressing the duodenum, a transcystic cholangiogram catheter introduces air into the biliary system. Bubbles along the cut surface identify the location of biliary leaks, which can be controlled with suture.

Minimally Invasive Surgery

Advances in minimally invasive techniques have permitted the extension of many of the benefits of minimally invasive surgery to be applied to patients undergoing liver resection. Although randomized controlled trials have not been performed, multiple retrospective case-control studies suggest that minimally invasive approaches are associated with similar margin-negative resection rates and oncologic outcomes. Moreover, laparoscopic liver resection is associated with less intraoperative blood loss, lower transfusion rates, and less opioid use as well as shorter length of hospital stay. Nevertheless, a significant learning curve exists as surgeons must be proficient in both open hepatobiliary surgery as well as advanced minimally invasive skills. Surgeons early in their learning curve will likely select patients with tumors in more favorable segments (II, III, IVb, V, and VI). As their experience progresses and skills improve, major hepatectomies and minor hepatectomies located in the posterosuperior segments (I, IVa, VII, and VIII) can be undertaken (Fig. 60-3). Minimally invasive liver resection can be performed either laparoscopically or robotically depending on the comfort and experience of the surgical team.

IMPROVEMENTS IN PERIOPERATIVE OUTCOMES

Several recent reports have demonstrated significant improvements in perioperative outcomes over time at experienced hepatobiliary centers. For example, at the Memorial Sloan-Kettering Cancer Center, the 90-day mortality rate decreased from 5.0% to 1.6% and morbidity rates decreased from 53% to 20% over the past 2 decades.29 The authors considered much of this improvement to be the result of a decrease in the proportion of patients undergoing major hepatectomy. On the other hand, a similar decrease in postoperative morbidity and mortality has been observed over time at the University of Texas MD Anderson Cancer Center but with concomitant increases in case complexity (unpublished data). Emerging evidence suggests that minimizing postoperative complications is important for optimizing patient-centered outcomes, returning patients expeditiously to intended
oncologic therapy, and potentially reducing recurrence rates.\textsuperscript{30-32} Significant volume-outcomes relationships have been observed in hepatobiliary surgery, and in general, major liver resections should be performed at high-volume experienced centers.

The factors contributing to improved perioperative outcomes are multifactorial. Patient selection and optimization, as discussed earlier in the chapter, are paramount. Anesthetic considerations are also important. Low central venous pressure (CVP) anesthesia is a central tenet for performing safe liver resection. Efforts at reducing intraoperative blood loss and perioperative transfusions are imperative as both are associated with increased complications and higher recurrence rates. In general, among patients with normal liver function who are receiving low-CVP anesthesia and meticulous surgical technique, the need for blood transfusion should be relatively rare. The quality of surgery is also important because remnant liver ischemia (RLI), which can occur via inadvertent vascular injury or imprecise surgery that leaves nonperfused liver tissue, is associated with perioperative complications as well as worse recurrence-free survival.\textsuperscript{33-35} Finally, established postoperative care pathways, including enhanced recovery protocols, are associated with high patient satisfaction and reductions in hospital length of stay.\textsuperscript{36} Multimodal analgesia is an important component of postoperative pathways because good pain control is associated with improved pulmonary function and reduced complications after hepatectomy.\textsuperscript{37}

**MULTIDISCIPLINARY CARE**

A major emphasis in the management of patients with benign and malignant liver diseases is the implementation of specialized multidisciplinary care. Patients with liver pathology and those under consideration for liver resection are best served by multidisciplinary evaluation from dedicated hepatobiliary surgeons, transplant surgeons, hepatologists, medical oncologists, radiation oncologists, radiologists, pathologists, and interventional radiologists. Advances in these fields have accompanied the myriad improvements observed in liver resection over the past several decades.

**Chemotherapy**
Improvements in survival for patients with CRLM are largely due to advances in systemic chemotherapy effective at treating colorectal cancer. Modern-day chemotherapy regimens using fluorouracil with either oxaliplatin or irinotecan are effective at downstaging some unresectable liver metastases to resectable. Newer targeted agents, such as the EGFR inhibitors cetuximab and panitumumab, may facilitate an even greater response among patients with KRAS wild-type tumors. Effective chemotherapy is critical for ensuring that systemic control of disease has been achieved (or is at least achievable) prior to performing major liver surgery. In addition, maintenance chemotherapy may allow relatively indolent stages of metastatic disease (eg, low volume lung or nodal metastases) to be controlled such that aggressive surgical resection can be focused on CRLM, which tends to be the most dominant factor in patient prognosis.

The routine use of preoperative systemic chemotherapy for resectable CRLM remains somewhat controversial. Although the European Organization for Research and Treatment of Cancer (EORTC) 49083 randomized controlled trial demonstrated a 9% improvement in progression-free survival among patients with resectable CRLM who received perioperative chemotherapy, given the absence of an overall survival benefit, many centers continue to recommend surgery alone, especially for patients with favorable prognostic features (eg, KRAS wild type, solitary lesion, metachronous). Two important principles regarding liver resection following chemotherapy are worthy of mention. First, rates of chemotherapy-associated liver injury (CALI) and PHI significantly increase after 6 cycles (ie, 12 weeks) of chemotherapy, so direct and frequent communication among surgeons and medical oncologists is imperative. Second, a subset of patients who receive preoperative chemotherapy will have a complete radiographic response leading to the so-called “disappearing liver metastasis.” Since a significant proportion of these lesions still harbor occult microscopic disease and many will eventually recur, surgical resection of disappearing metastases is typically recommended when feasible.

Given the lack of effective systemic options, the routine use of preoperative chemotherapy is not indicated for primary liver cancers, although combination gemcitabine/cisplatin can downstage unresectable cholangiocarcinoma to resectable in a minority of cases. Regarding
noncolorectal liver metastases (eg, breast, genitourinary, sarcoma), the demonstration of favorable tumor biology via a positive radiographic response in the metastasis or at least stability of disease will identify patients most likely to benefit from liver resection. Ultimately, the long-term outcomes of liver resection will depend on availability of effective nonsurgical therapies.

Liver-Directed Therapies

A surge in the availability and efficacy of liver-directed therapies has improved the multidisciplinary care of patients with primary and metastatic liver cancers, resulting in improved outcomes for patients with both resectable and unresectable liver tumors. For example, transarterial chemoembolization (TACE) is now commonly employed for downstaging and bridging patients with HCC to liver transplantation, whereas hepatic arterial infusion therapy with implantable pumps can successfully downstage patients with initially unresectable CRLMs. In addition, nonsurgical techniques (eg, ablation) are frequently combined with surgical resection as part of a comprehensive multidisciplinary treatment strategy for bilobar CRLM (Fig. 60-4). At the same time, the availability of effective nonsurgical options, such as TACE, ablation, or radioembolization with yttrium-90, has permitted the careful selection of patients with HCC most likely to benefit from safe surgical resection (eg, Child A with preserved liver function or Barcelona Clinic Liver Cancer stage 0). Finally, liver-directed therapies are critical for treating recurrent liver tumors not amenable to repeat hepatectomy. Combined with effective systemic chemotherapy, these therapies can contribute to extended overall survival durations even for patients with recurrent unresectable disease.
FIGURE 60-4 A systematic algorithm for assessing the distribution and extent of bilateral colorectal liver metastases that informs operative treatment strategy. Each scenario is modeled with the right liver in blue (representing approximately 65% of total liver volume) and the left liver in red (representing approximately 35% of total liver volume). Tumors are represented as closed circles, parenchymal sparing resections as open circles, and ablations as open stars. HAI, hepatic arterial infusion; PSH, parenchymal sparing hepatectomy; PVO, Portal vein occlusion; RH, right hepatectomy. (Reproduced with permission from Cloyd JM, Aloia TA: Hammer versus Swiss Army knife: Developing a strategy for the management of bilobar colorectal liver metastases, Surgery 2017 Jul;162(1):12-17.)

Hepatobiliary surgeons should be abreast of the indications for, the technical aspects of, and the expected outcomes of various liver-directed therapies for primary and metastatic liver tumors. As part of a comprehensive multidisciplinary program that includes expertise in hepatic surgery, improvements in liver-directed therapies have greatly improved the outcomes of patients with complex liver pathology. These patients are therefore best evaluated and managed at tertiary care centers with multidisciplinary specialization and access to the latest knowledge, techniques, and clinical trials.
FUTURE DEVELOPMENTS

At the same time as an improved understanding of tumor biology has led to more effective systemic and liver-directed therapies, simultaneous advances in our knowledge of liver anatomy, FLR assessment and augmentation, liver resectional techniques, and perioperative care have enabled the application of safe, oncologically sound hepatic resection to an increasing number of patients. Due to ongoing translational research, further practice-changing advances are expected. An improved understanding of the molecular biology of liver cancers should not only result in new targeted therapies, but also an opportunity to personalize therapy according to specific molecular features. Already, certain somatic mutations are known to affect prognosis in CRLM and may influence the therapeutic strategy accordingly. Improvements in systemic and liver-directed therapies should aim to more effectively downstage patients such that liver resection can be applied more broadly. An understanding of which patients who develop a complete radiographic response require surgical resection would also be instructive.

Advances in diagnostic imaging will assist not only in tumor identification and diagnosis, but also in accurate assessment of the FLR. At the same time, improvements in augmentation strategies or even bioartificial liver replacement strategies (eg, xenotransplantation, liver tissue engineering, cell transplantation) may afford an opportunity to offer surgical resection to patients who currently have inadequate FLR volume or function. Real-time image guidance technologies are currently available, but future improvements in registration and tracking techniques as well as the development of state-of-the-art operating rooms with upgraded imaging technology will be needed before image navigation is routinely used. Similarly, advances in minimally invasive technology beyond current laparoscopic and robotic systems should enable a faster learning curve and allow the benefits of minimally invasive hepatic surgery to be applied more broadly.

SUMMARY

The field of liver surgery is rapidly changing. Evolving indications for resection, enhanced FLR assessment tools, advances in surgical technique and perioperative care, new systemic and liver-directed therapies, and an improved molecular and biological understanding of liver tumors suggest that
patients are best managed in experienced multidisciplinary centers. In this evolving landscape, surgeons should continue to lead efforts at identifying the optimal treatment strategies for patients with both primary and metastatic tumors of the liver.

REFERENCES


PORTAL HYPERTENSION

Douglas W. Hanto • Sunil K. Geevarghese • Christopher Baron

INTRODUCTION

Portal hypertension (PHTN) can occur in cirrhotic and noncirrhotic patients and can be classified as presinusoidal or prehepatic (extrahepatic or intrahepatic), sinusoidal or hepatic, or post-sinusoidal or post-hepatic (Fig. 61-1). Portal pressure can be measured directly, or more commonly indirectly, by calculating the hepatic vein pressure gradient (HVPG) by subtracting the measured free hepatic vein pressure (FHVP) from the wedged hepatic vein pressure (WHVP). Portal pressure is normally <6 mm Hg and clinically significant PHTN is defined as an HVPG greater than 10 to 12 mm Hg (Table 61-1).
FIGURE 61-1 Portal hypertension and sites of obstruction.

TABLE 61-1: PORTAL HYPERTENSION

Hepatic vein pressure gradient (HVPG) = Wedged hepatic vein pressure (WHVP) – Free hepatic vein pressure (FHVP)
Normal: HVPG <6 mm Hg
Clinically significant portal hypertension: HVPG >10-12 mm Hg

The most common complications of PHTN include gastroesophageal varices, portal hypertensive gastropathy, splenomegaly and hypersplenism, ascites, hepatic hydrothorax, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, and cirrhotic
cardiomyopathy (Table 61-2). The management of PHTN has changed dramatically over the past two decades and has been the subject of several clinical practice guideline publications.

Medical, endoscopic, and radiologic management strategies have largely replaced many surgical procedures such as selective and nonselective shunts, devascularization procedures, and peritoneovenous shunts. This chapter emphasizes the role of current therapies in the management of patients with PHTN and its complications.

**TABLE 61-2: COMPLICATIONS OF PORTAL HYPERTENSION**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Gastric varices</td>
<td>Hepatic encephalopathy</td>
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<tr>
<td>Esophageal varices</td>
<td>Hepatorenal syndrome</td>
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<tr>
<td>Portal hypertensive gastropathy</td>
<td>Hepatopulmonary syndrome</td>
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<td>Splenomegaly and</td>
<td>Portopulmonary hypertension</td>
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<td>hypersplenism</td>
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<tr>
<td>Ascites</td>
<td>Cirrhotic cardiomyopathy</td>
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<tr>
<td>Hepatic hydrothorax</td>
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</tbody>
</table>

**HISTORY**

Although descriptions of PHTN and its complications go back over four centuries, surgical therapy was pioneered by Nicolai Eck, who first performed an end-to-side portacaval shunt in an animal model in 1883. Pavlov described hepatic encephalopathy, referred to as meat intoxication at the time, as a consequence of diverting portal flow, which he believed was due to nitrogenous compounds that were not being cleared by the liver. The first portosystemic shunt in a human was performed by Vidal in 1903, but Whipple and colleagues pioneered the era of surgical decompression of portal hypertension in the 1940s. In the 1960s and 1970s, Drapanas developed the mesocaval shunt, Warren and Inokuchi developed selective variceal bed decompression with the distal splenorenal and coronary vein-caval shunts, respectively, Sarfeh studied and popularized small diameter H-grafts, and Sugiura pioneered gastroesophageal devascularization and splenectomy. In the 1980s, endoscopic sclerotherapy and band ligation were introduced for control of variceal hemorrhage. The subsequent development of
pharmacologic therapy, transjugular intrahepatic portosystemic shunts (TIPS), and the pioneering work of Starzl and Calne in the 1960s and 1970s, making liver transplantation a viable alternative for patients with end-stage liver disease, have all radically transformed the care of these patients.

**PATHOPHYSIOLOGY**

Portal hypertension results from increased resistance to portal flow in association with increased portal collateral flow. The increased resistance occurs most commonly within the liver due to cirrhosis, but it can occur prehepatic as in portal vein thrombosis (PVT) or post-hepatic due to obstruction of hepatic venous flow (Budd–Chiari syndrome or veno-occlusive disease) ([Fig. 61-1](#)). Rarely, a hepatic arterial-portal venous fistula can cause PHTN.

As Bleibel et al. have noted, resistance to portal flow is the result of structural as well as physiologic derangements. Under normal physiologic conditions there is little resistance to portal venous flow and there is little intrinsic regulation of portal flow. In cirrhosis, however, collagen deposition and fibrosis, along with the contractile properties of stellate cells and myofibroblasts that surround the hepatic sinusoids and reside in fibrous septa along with vascular smooth muscle cells, lead to an increased resistance to portal flow. Initially, the splanchnic vascular bed response is vasoconstriction due to the release of thromboxane A2, norepinephrine, endothelins, and angiotensin-II, along with decreased nitric oxide–mediated vasodilatation. With progression of portal hypertension, the release of splanchnic vasodilators such as nitric oxide and vascular endothelial growth factor predominates, resulting in increased splanchnic inflow.

These changes result in the development of collaterals between the portal and systemic circulations ([Fig. 61-2](#)), plasma volume expansion, increased cardiac output, systemic vasodilatation, and hypotension. The development of a systemic hyperdynamic circulation results in systemic blood pressures of 100 to 110 mm Hg, cardiac outputs ranging from 10 to 15 L/min, and low calculated systemic vascular resistance of 250 to 500 dynes/cm$^5$ that can impact fluid resuscitation and patient management.
ETIOLOGY AND CLINICAL PRESENTATION

In developed countries, 90% of patients with PHTN have cirrhosis most often caused by chronic viral hepatitis (hepatitis B, C), alcoholic liver disease, hemochromatosis, and nonalcoholic steatohepatitis. Less common causes include autoimmune hepatitis, primary and secondary biliary cirrhosis, primary sclerosing cholangitis, medications (eg, methotrexate), Wilson disease, α-1 antitrypsin deficiency, celiac disease, idiopathic adulthood ductopenia, granulomatous liver disease, idiopathic portal fibrosis, polycystic
liver disease, right-sided heart failure, Budd–Chiari syndrome, and veno-occlusive disease (Table 61-3). A smaller percentage of patients will have noncirrhotic PHTN usually caused by PVT or hepatic fibrosis. In other parts of the world, noncirrhotic PHTN is much more common and is most often caused hepatic schistosomiasis or PVT.

<table>
<thead>
<tr>
<th>Prehepatic</th>
<th>Prehepatic</th>
<th>Hepatocellular</th>
<th>Post-Hepatic</th>
<th>High-Flow</th>
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<td>Extrahepatic</td>
<td>Intrahepatic</td>
<td>Post-infectious cirrhosis (HCV, HBV)</td>
<td>Budd-Chiari syndrome</td>
<td>Arteriovenous communication— intrahepatic or extrahepatic</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
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<td>Alcoholic liver disease</td>
<td>Veno-occlusive disease</td>
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<td>Sarcoïdosis</td>
<td>Nonalcoholic steatohepatitis (NASH)</td>
<td>Constrictive pericarditis</td>
<td>Vena caval webs</td>
</tr>
<tr>
<td>Superior mesenteric vein thrombosis</td>
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<td>Biliary atresia</td>
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<td>Congenital disorders of bile acid metabolism</td>
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<td>Congenital hepatic fibrosis</td>
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<td></td>
<td></td>
<td>Nodular regenerative hyperplasia</td>
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<td></td>
<td></td>
<td>Primary sclerosing cholangitis</td>
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<td></td>
<td></td>
<td>Primary biliary cirrhosis</td>
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<td></td>
<td></td>
<td>Autoimmune hepatitis</td>
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<td></td>
<td></td>
<td>Drug toxicity</td>
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<td></td>
<td>(eg, methotrexate)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Metabolic diseases</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(eg, α-1-antitrypsin)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Hemochromatosis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Wilson disease</td>
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</tbody>
</table>

Patients with cirrhosis are often asymptomatic even though 80% have an elevated HVPG and nearly 50% will have esophageal varices. Patients with PHTN and no varices will develop varices at a rate of about 8% per year. Patients come to the attention of their physician as the complications noted in the introduction develop (Table 61-2). Briefly, the clinical manifestations of bleeding gastroesophageal varices are usually hematemesis and/or melena, but can present with shock and vascular collapse from exsanguinating hemorrhage. Portal hypertensive gastropathy is manifest as diffuse mucosal oozing and may present with anemia from chronic blood loss. Splenomegaly and hypersplenism may present with leukopenia, thrombocytopenia, and sometimes anemia. Ascites, the buildup of fluid in the peritoneal cavity, may
present with abdominal distention, weight gain, and shortness of breath from
the increased fluid and intra-abdominal pressure. Patients can also develop
hydrothorax (pleural effusion) from movement of fluid from the abdominal
cavity into the pleural space, usually on the right side. They can also present
with spontaneous bacterial peritonitis with fever, pain, and tenderness.
Patients often first present with confusion or hepatic encephalopathy that can
be precipitated by many factors including bleeding, infection, renal failure,
and other manifestations of liver failure. Hepatorenal syndrome is the
development of renal insufficiency in patients with cirrhosis. Patients with
hepatopulmonary syndrome may be asymptomatic in its early stages, but may
present with oxygen desaturation, shortness of breath, and dyspnea on
exertion caused by intrapulmonary shunting. Patients with portopulmonary
hypertension may have similar symptoms related to elevated pulmonary
artery pressures.

The severity of liver decompensation can be characterized by the Pugh-
modified Child-Turcotte (Child-Turcotte-Pugh [CTP]) classification scheme
(Table 61-4) or the Model for End-Stage Liver Disease (MELD) score
(Table 61-5) (discussed later). The CTP score, which uses clinical assessment
and laboratory values, has been used to determine the functional status of the
liver and estimate liver reserve as well as predict morbidity and mortality
after shunt surgery and other general surgical procedures in cirrhotic
patients. Patients with Child A cirrhosis have adequate liver reserve and
tolerate shunt and general surgery with survival rates similar to noncirrhotic
patients. On the other hand, Child C patients have a high mortality, often
exceeding 50%, and in general are not candidates for shunt or general
surgical procedures, but are candidates for liver transplantation. The CTP has
been largely replaced with the MELD score that was originally developed to
predict the mortality for cirrhotic patients undergoing TIPS and has been
adapted to predict the mortality of patients on the liver transplant waiting list
and to prioritize liver allocation to the sickest patients.

| TABLE 61-4: PUGH MODIFIED CHILD-TURCOTTE CLASSIFICATION |
TABLE 61-5: MODEL FOR END-STAGE LIVER DISEASE (MELD)

<table>
<thead>
<tr>
<th></th>
<th>One Point</th>
<th>Two Points</th>
<th>Three Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily</td>
<td>Poorly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>controlled</td>
<td>controlled</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
<td>1 or 2</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>1-4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>(prolonged) or INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>For primary biliary cirrhosis: bilirubin (mg/dL)</td>
<td>1-4</td>
<td>4-10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
For each of five items a score of 1, 2, or 3 is assigned. Total score is summed.
Child’s A = 5-6, B = 7-9, C = 10-15.

MELD = 3.78 × ln[serum bilirubin (mg/dL)] + 11.2 × ln[INR] + 9.57 × ln[serum creatinine (mg/dL)] + 6.43

The 3-month mortality for a patient undergoing a TIPS with a MELD score of 40 or more is 71.3%, 30-39 is 52.6%, 20-29 is 19.6%, 10-19 is 6.0%, and <9 is 1.9%.

DIAGNOSTIC EVALUATION

The goals of diagnostic studies in initially evaluating patents with PHTN and its complications are to determine the presence of hepatic disease, the level of obstruction to flow, the presence and extent of intra-abdominal portosystemic collaterals, the direction of blood flow in the portal vein (PV) (hepatopetal, toward the liver; hepatofugal, away from the liver), as well as the presence of thrombosis. The imaging is typically multimodality, including duplex ultrasound (US) and multiphase computed tomography (CT) as well as multiphase magnetic resonance imaging (MRI), and conventional angiography. CT arteriography (CTA), CT venography (CTV), MR
angiography (MRA), and MR venography (MRV) can also be useful in certain circumstances.

**Duplex Ultrasound**

Duplex US, which includes both gray scale and color Doppler sonography, is a noninvasive, portable, and inexpensive technique that does not use ionizing radiation and is frequently used as the first-line examination in the diagnosis and follow-up of patients with liver disease and PHTN. Grayscale interrogation of the liver is used to evaluate overall morphology as well as to locate focal lesions suggestive of hepatocellular carcinoma. Color Doppler US is useful in evaluation of the portal, splenic, hepatic, and superior mesenteric veins, the vena cava, and the hepatic artery, including flow direction, flow velocity, and large vessel thrombosis. Portosystemic collaterals are readily identified, and findings such as paraumbilical veins, spontaneous splenorenal circulation, dilated left and short gastric veins, and hepatofugal flow within the portal system are 100% specific US signs of clinically significant PHTN. Duplex US is also useful in identifying causes of PHTN other than cirrhosis, such as portal or hepatic vein thrombosis. In a recent prospective study, a PV average maximum velocity of <15 cm/s was the only variable independently associated with a high risk of nonmalignant PVT. Splenomegaly (diameter >12 cm and/or area >45 cm²) is the most commonly associated and sensitive sign of the presence of PHTN, is an independent predictor of esophageal varices, and is associated with clinically significant PHTN in compensated cirrhotic patients.

Other US signs of clinically significant PHTN include dilatation of the PV (diameter >13 mm), lack of or reduced respiratory variations of splenic and superior mesenteric vein (SMV) diameter, lack of respiratory caliber variations in one of the major portal tributaries (splenic vein [SV] and/or SMV), reduced PV velocity (maximal and mean velocity of PV flow, respectively <16 cm/s and <10 to 12 cm/s), increased congestion index of PV (ratio between the cross-sectional area and blood flow velocity), altered hepatic venous Doppler pattern, increased intraparenchymal hepatic and renal artery impedance, and reduced mesenteric artery impedance.

Finally, Duplex US is useful in the surveillance of patients who have been decompressed by TIPS. Doppler US evaluation can diagnose TIPS.
dysfunction by demonstrating in-stent velocities >250 cm/s or <50 cm/s with greater than 90% sensitivity and specificity.\textsuperscript{20}

**Multiple-Detector Computed Tomography, CT arteriography, CT venography**

Multiple-detector computed tomography (MDCT) uses ionizing radiation to acquire a volumetric data set that allows three-dimensional multiplanar reconstructions. Noncontrast images are acquired, intravenous contrast administered, and dynamic images are acquired in the hepatic arterial phase (12 sec following injection), portal venous phase (55 sec following injection), and finally in the late venous phase (120 sec following injection).\textsuperscript{21}

MDCT can identify morphologic changes including hepatomegaly in the early stages of cirrhosis. In the later stages, there is frequent atrophy of the right lobe and medial segment of the left lobe with hypertrophy of the left lateral segment. MDCT can also characterize regenerative nodules, dysplastic nodules, and hepatocellular carcinoma (HCC), determine the patency of the venous and arterial systems, and measure liver volumes, which can be useful in preoperative planning for liver transplantation.

Portosystemic collaterals (varices) develop as portal pressures rise above 10 mm Hg, are a hallmark of PHTN, and appear as enhancing, well-defined tubular or serpentine structures that follow the enhancement characteristics of the PV. The left gastric (coronary) vein (LGV) is the most commonly seen portosystemic collateral and is dilated in up to 80% of cirrhotic patients. It normally drains the anterior and posterior surfaces of the stomach and ascends the lesser curvature to the gastroesophageal junction, where it receives the esophageal vein and supplies esophageal and paraesophageal varices that drain into the azygous/hemizygous venous systems.\textsuperscript{22} The LGV drains into the PV at the superior border of the duodenum. Dilated left gastric veins are visible between the anterior wall of the stomach and the posterior surface of the left hepatic lobe. A left gastric vein size larger than 5 to 6 mm or multiple veins 4 to 6 mm in diameter are indicative of PHTN. A left gastric vein greater than 7 mm has been shown to correspond to a HVPG of 10 mm Hg.\textsuperscript{23} Approximately 30% to 70% of patients with PHTN develop varices and 9% to 36% are considered “high risk.”\textsuperscript{24}

Paraumbilical venous collaterals are found in 43% of patients with PHTN.
They appear as tubular enhancing structures in the falciform ligament and are supplied by the left PV via a recanalized umbilical vein. They connect with the superior epigastric vein and/or internal thoracic veins which drain into the superior vena cava or connect with the inferior epigastric vein that drains into the external iliac vein. These abdominal wall varices form the caput medusae that are seen on physical exam as dilated subcutaneous veins at the umbilicus.

Gastric varices form in the face of PHTN and decreased drainage through the left gastric, posterior gastric, and short gastric veins. In this setting, portosystemic shunting can be through the left inferior phrenic or left adrenal veins forming a gastrorenal shunt. The incidence of gastric varices in patients with PHTN is approximately 30%. Retroperitoneal varices are commonly seen collaterals and form between intestinal or retroperitoneal tributaries of the SMV or IMV and the systemic circulation.

PVT may be present in 1% of patients with early cirrhosis, in 30% of patients with advanced cirrhosis who are candidates for liver transplantation, and in 10% to 40% of patients with HCC, as well in patients with no cirrhosis but who may have a hypercoagulable state. PVT is demonstrated by an intraluminal filling defect on US (Fig. 61-3A) and on CTA after the administration of IV contrast (Fig. 61-3B, C), and can be associated with bowel ischemia (Fig. 61-3D). After PVT, there is rapid development of numerous enhancing venous collaterals in the porta hepatitis that bypass the obstruction, referred to as cavernous transformation.
FIGURE 61-3  Acute portal and mesenteric venous thrombosis with associated bowel ischemia in 43-year-old man with the onset of abdominal pain, nausea and vomiting one-week prior. Protein S deficiency and lupus anticoagulant were found. A. Gray scale sagittal US image of the right hepatic lobe demonstrates echogenic material filling the right PV indicating PVT (arrows). B. Axial contrast-enhanced multidetector CT shows non-enhancement of the right portal venous branches (arrows) consistent with thrombosis as well as perihepatic ascites (arrowheads). C. Coronal reformatted multidetector CT images depicts extension of thrombosis into superior mesenteric (arrows) and inferior mesenteric (arrowhead) veins.
Thrombotic extension into the splenic vein is also present (black arrow). D. Axial contrast-enhanced multidetector CT shows diffuse hyperattenuating small bowel wall thickening (white arrows), with mesenteric fat stranding (black arrows) and free fluid (arrowheads) corresponding to small bowel ischemia.

**Magnetic Resonance Imaging, MR Angiography, MR Venography**

MRI uses a high field-strength magnet in combination with radiofrequency energy to create three-dimensional images that can be viewed in multiple planes. Gadolinium chelates are used as contrast agents to improve tissue contrast and to perform angiography. Newer, liver-specific contrast agents such Eovist have been developed, with up to 50% of the injected dose of these liver-specific agents taken up by functioning hepatocytes and excreted in the bile. As with MDCT, MR imaging of patients with diffuse liver disease and PHTN is a dynamic process; T1 in-phase and out-of-phase, T2, and diffusion-weighted sequences are performed. Post-contrast studies are acquired in the arterial phase (20-35 sec), portal phase (70 sec), and equilibrium phase (3 min). A fourth phase is added with liver-specific agents and a delayed hepatobiliary phase at 20 minutes.  

MRA can be performed using multiple techniques both with and without the administration of gadolinium contrast agents, and has an added benefit over MDCT in that it can provide information on both flow direction and flow velocity. MRI/MRV has proven useful in the evaluation of the portosystemic collaterals and the vena cava and evaluation of PVT, and compares equally to MDCT. MRI performs equally as well as MDCT in the diagnosis of HCC, but has increased accuracy in detecting smaller lesions.

**Endoscopy**

Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of esophageal and gastric varices and variceal hemorrhage (Fig. 61-4A-D). It is recommended that esophageal varices be classified as small (<5 mm in diameter) or large (>5 mm in diameter), with the large varices including medium-sized varices when three grades are used (small, medium, and large).
Care should be taken to document the presence or absence of red signs (red wale marks or red spots) on varices that identify high-risk varices. Because therapy with β-blockers prevents bleeding in more than half of patients with medium or large varices, it is recommended that newly diagnosed patients with cirrhosis undergo screening EGD for varices. The prevalence of medium/large varices is about 15% to 25%, so most patients will have a negative EGD or have varices that do not warrant prophylactic treatment. Other noninvasive markers of varices such as platelet count, FibroTest, spleen size, PV diameter, and transient elastography have so far been inaccurate and cannot substitute for screening EGD. It is recommended that patients with no varices and compensated cirrhosis should undergo repeat EGD in 2 to 3 years. Patients with small varies should undergo repeat EGD in 1 to 2 years. Patients with decompensated cirrhosis should have yearly EGD. Esophageal capsule endoscopy may play a role in the future in screening for esophageal varices, although it is still not as sensitive as EGD.27
Angiography and Measurement of Hepatic Venous Pressure Gradient

Historically, angiography played a larger role in the evaluation of patients with PHTN. The portal venous system was indirectly evaluated in the venous phase of celiac or superior mesenteric artery angiography or directly imaged through splenoportography or through transhepatic or transjugular portal venography (Fig. 61-5). However, with the advent of cross-sectional imaging, these diagnostic techniques are now rarely used.
Angiography still plays an important role in measurements of the HVPG that is an indirect measurement of portal venous pressure. The procedure is usually performed from a jugular vein access. The inferior vena cava (IVC) is cannulated with a diagnostic catheter and the right hepatic vein is subselected. If using a straight, end hole catheter, it is advanced peripherally into the hepatic vein until wedged, rendering the WHVP. Pressure measurements are obtained with the transducer at the right atrial level (mid-axillary line). A subsequent injection of contrast confirms the location by visualization of a characteristic sinusoidal pattern. The catheter is then withdrawn into the hepatic vein, and an FHVP is obtained. Alternatively, a balloon-tipped catheter is advanced into the middle third of the right hepatic vein and inflated to occlude the vein, which allows measurement of the WHVP. Again, injection of contrast with the balloon inflated confirms balloon occlusion of the hepatic vein. The FHVP is obtained after deflating the balloon. A prospective trial compared these two techniques against direct portal pressure measurements and found that that the balloon occlusion
method is more reproducible and more accurately reflects the direct portal pressure.\textsuperscript{28}

The HVPG is calculated by subtracting the FHVP from the WHVP, which eliminates the changes in the pressure measurements caused by changes in intra-abdominal pressure. At the time of pressure measurements, transjugular liver biopsy can also be safely performed and is particularly advantageous in patients who do not meet criteria for percutaneous or open liver biopsy because of uncorrectable coagulopathy or ascites.\textsuperscript{29}

A normal HVPG is less than 6 mm Hg, and clinically significant PHTN develops at pressures of 10 to 12 mm Hg with the development of varices. Significant complications such as variceal bleeding and ascites usually arise at pressures greater than 12 mm Hg.\textsuperscript{30}

COMPlications of portal Hypertension

Ascites

Approximately 85\% of patients in the United States with ascites have cirrhosis, and 15\% have nonhepatic etiologies including cancer, heart failure, tuberculosis, or nephrotic syndrome.\textsuperscript{31} Ascites is usually suspected on the basis of the history and physical examination and confirmed by ultrasound and by paracentesis. Ascites from PHTN can easily be differentiated from other causes by straightforward fluid analysis. The diagnosis of spontaneous bacterial peritonitis (SBP) can be made by determining the absolute number of PMNs in the fluid (>250 PMNs per mm\textsuperscript{3}).

MedicAl Management

Recommendations for medical management of ascites include abstinence from alcohol if this is the cause of liver disease. Additional recommendations include sodium restriction and diuretics (spironolactone and furosemide), fluid restriction if the serum sodium is less than 120 to 125 mmol/L, and an initial therapeutic paracentesis in patients with tense ascites (Fig. 61-6). Patients who respond to diuretics are preferentially treated with sodium
restriction and diuretics rather than serial paracentesis.\textsuperscript{31} Patients with cirrhosis and ascites should be considered for liver transplantation.

![FIGURE 61-6 Sites for paracentesis.](image)

Patients have refractory ascites if they have fluid overload that is unresponsive to sodium restriction and high-dose diuretics or recurs quickly after undergoing therapeutic paracentesis. Treatment options include serial therapeutic paracentesis, TIPS, peritoneovenous shunt, or liver transplantation.

Controlled trials of serial large volume (5-10 liters) therapeutic paracentesis demonstrating its effectiveness and safety have been published\textsuperscript{32} and may be performed as often as biweekly or weekly. Although the administration of albumin after large-volume paracentesis is of uncertain value, it is recommended that an albumin infusion of 6 to 8 g/L of fluid be considered, particularly for volumes greater than 5 liters.\textsuperscript{31}
**SURGICAL MANAGEMENT**

Patients with refractory ascites should be referred for liver transplantation unless there are other surgical or medical contraindications, because 21% die within 6 months. Peritoneovenous shunts (LeVeen or Denver shunts) currently have few indications because of their poor long-term patency due to a high incidence of thrombotic, infectious, and technical complications. Furthermore, controlled trials have demonstrated no survival advantage compared to medical management. Peritoneovenous shunts are now reserved for patients who are not candidates for serial paracentesis (eg, distance from a physician able to perform the procedure) and for patients who are not candidates for liver transplantation or TIPS.

**RADIOLOGIC MANAGEMENT**

**Ultrasound.** Although paracentesis in patients with massive ascites can be safely and easily performed without US guidance, in patients who are obese or otherwise have fluid that is difficult to localize by physical examination, paracentesis can be aided by performance under US guidance.

**Transjugular Intrahepatic Portosystemic Shunt.** The development of refractory ascites, which occurs in 5% to 10% of patients with ascites, is associated with a 1-year mortality of 50% to 90% and is a common indication for liver transplantation. By reducing portal pressure, TIPS (discussed in more detail in the section on varices) has been shown to be effective in managing patients with refractory ascites.

A meta-analysis of five randomized control trials by D’Amico et al. demonstrated a 7.1-fold reduction in the risk of recurrence of tense ascites after TIPS. Rates of improvement ranged from 38% to 84% after TIPS compared to 0% to 43% after large volume paracentesis. There was a trend toward a reduction in mortality in the TIPS group. Rates of hepatic encephalopathy were 2.2-fold higher in TIPS patients compared to repeated large-volume paracentesis. A meta-analysis by Salerno et al. and review by Eesa et al. also demonstrated TIPS to be superior to repeated large-volume paracentesis in controlling ascites and was associated with a significantly better transplant-free survival at 12 and 24 months.

The threshold portosystemic gradient (PSPG) (see section on TIPS for
treatment of variceal hemorrhage) in the treatment of patients with refractory ascites has been a subject of some debate. The Society of Interventional Radiology (SIR) and American Association for the Study of Liver Disease (AASLD) guidelines recommended reducing the PSPG to less than 8 mm Hg.  

**Hepatic Hydrothorax**

Hepatic hydrothorax develops in patients with cirrhosis and ascites when there is direct communication between the abdominal and thoracic cavities. It may develop in patients without clinically evident ascites. In most patients the defect is over the dome of the liver. The use of TIPS in the treatment of hepatic hydrothorax is supported by several retrospective case series describing the outcomes of more than 150 patients. At least partial improvement in clinical symptoms (dyspnea and decrease in frequency of thoracentesis) has been reported in 68% to 82% of patients, whereas complete resolution of hydrothorax was observed in 57% to 71% of patients.

**Gastric and Esophageal Varices**

Gastroesophageal varices occur in patients with cirrhosis and PHTN with an HVPG of at least 10 to 12 mm Hg. They are present in 50% of patients with cirrhosis, but their incidence is associated with the severity of the liver disease, ranging from 40% in patients with compensated cirrhosis to 85% in patients with decompensated cirrhosis. Varices develop at a rate of 8% per year in patients without varices, and the HVPG is the strongest predictor for their development.  

Variceal hemorrhage is the most life-threatening complication of portal hypertension and occurs at a yearly rate of 5% to 15% and at an overall rate of 25% to 70% (Fig. 61-7). Large varices on EGD and the presence of cherry red spots and red wale marks—linear, dilated venules that endoscopically look like whip marks on the variceal surface—are associated with a higher risk of hemorrhage (Fig. 61-4B, C), as is the degree of elevation of the HVPG. In spite of improvements in care, the mortality of esophageal variceal hemorrhage is still about 20%, but exceeds 60% in patients with HVPG >20 mm Hg. This is in part related to the fact that patients with an
HVPG >20 mm Hg are at increased risk for early rebleeding or inability to control bleeding. Overall for survivors of a first bleed, 30% will rebleed within 6 weeks, and by 1 to 2 years nearly 60% will have rebled.\textsuperscript{42,43} Gastric varices are less common (5%-33%) than esophageal varices in patients with PHTN and about 25% will bleed over 2 years.

\textbf{FIGURE 61-7} Bleeding esophageal varix seen on EGD in a patient with hematemesis.

\textbf{MEDICAL MANAGEMENT}

\textbf{Prophylaxis.} Preventive management of variceal hemorrhage includes pharmacologic and endoscopic therapy. Nonselective $\beta$-blockade involves $\beta_1$ and $\beta_2$ adrenergic blockades, which are known to decrease cardiac output ($\beta_1$) and increase splanchnic arteriolar vasoconstriction ($\beta_2$), reducing portal flow (eg, propranolol and nadolol) (Table 61-6). Vasopressin also has splanchnic vasoconstrictive properties and decreases portal venous collateral flow and portal pressure. Somatostatin decreases splanchnic flow, but does so indirectly by reducing glucagon, substance P, and vasoactive intestinal
peptide.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Portal Flow</th>
<th>Portal Resistance</th>
<th>Portal Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstrictors (eg, β-blockers)</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Venodilators (eg, nitrates)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Endoscopic therapy</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>TIPS/shunt</td>
<td>↑</td>
<td>↓↓↓↓</td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>

*Although theoretically nitrates act by decreasing resistance, they actually act by decreasing portal flow through a decrease in mean arterial pressure.*


Endoscopic therapy is an effective means of preventing and controlling variceal bleeding. Endoscopic variceal band ligation (EVL) can be performed at the bedside and has largely replaced endoscopic sclerotherapy (ES), which can be associated with fever, chest pain, dysphagia, and perforation. EVL has been compared to nonselective beta blockade in several randomized trials. Two meta-analyses have confirmed that it is associated with lower incidence of first variceal bleed without differences in mortality. EVL can be
performed regularly to manage the variceal burden in patients when combined with pharmacologic therapy. Per AASLD Practice Guidelines, it can be repeated every 1 to 2 weeks until obliteration. Surveillance EGD can then follow every 6 to 12 months.

**Variceal Hemorrhage.** The first-line treatment of variceal hemorrhage ([Fig. 61-7](#)), in addition to volume resuscitation with fluid and blood, and replacement of clotting factors and platelets, is pharmacologic therapy with intravenous vasopressin and nitroglycerin, terlipressin, somatostatin, or octreotide prior to EGD and continued for 3 to 5 days. Patients should also be started on antibiotic prophylaxis with ciprofloxacin or ceftriaxone ([Fig. 61-8](#)).

EGD should be performed within 12 hours, and EVL performed to control bleeding ([Fig. 61-9](#)). EVL controls bleeding in approximately 80% to 100% of patients and has the same or better results than ES. Multiple follow-up sessions are required to eliminate the varices, and are generally performed.
every 1 to 2 weeks until obliteration. Rebleeding is less after EVL compared to ES \(^{46}\) (Fig. 61-10) and mortality is lower, so EVL is preferred.

**FIGURE 61-9** Endoscopic sclerotherapy (ES). Intravariceal injection (A) and paravariceal injection (B).
Balloon tamponade with a Sengstaken-Blakemore or Minnesota tube can be used for control of variceal hemorrhage in patients who are unresponsive to pharmacologic therapy and EVL. These tubes use two balloons—a gastric balloon and an esophageal balloon—to tamponade the submucosal veins. Initial control of bleeding is accomplished in 80% of patients, but over 50% rebleed after the balloons are deflated. However, these tubes can be used as a temporizing measure while preparing the patient for an emergent TIPS or surgical shunt (Fig. 61-11).
not required.

Gastric varices occur in 5% to 30% of patients with PHTN. Type 1 gastric varices are an extension of esophageal varices along the lesser curvature of the stomach, and management should be the same as for esophageal varices. The bleeding rate of gastric fundal varices has been reported to be up to 45% at 3 years.\textsuperscript{4,48,49} Gastric varices can be difficult to treat and there are few clinical trials to guide therapy. Treatment options include intravariceal injections of a number of sclerosants and “glues” including alcohol, thrombin, and N-butyl-cyanoacrylate (with N-butyl-cyanoacrylate preferred), EVL, TIPS, and balloon retrograde transvenous obliteration (BRTO). The threshold for TIPS placement is lower than for esophageal variceal hemorrhage and should be considered if EVL or sclerosis are not options or have failed on one occasion.

**SURGICAL MANAGEMENT**

The surgical management of PHTN has a storied past and at one time was the primary treatment modality. However, innovations in medical management, endoscopic therapies, percutaneous radiologic procedures such as TIPS, and the success of liver transplantation\textsuperscript{50} have nearly eliminated the need for surgical shunts except in very limited circumstances. These include symptomatic PHTN in the noncirrhotic patient with preserved liver function (eg, schistosomiasis), patients with Budd−Chiari syndrome, and patients with total mesenteric venous occlusion who may be candidates for splenopneumopexy or a devascularization procedure.

Two major groups of procedures are discussed below: decompressive operations, which can be divided into nonselective and selective shunts,\textsuperscript{2,51} and devascularization procedures. Nonselective shunts result in the diversion of portal venous blood from the liver into the systemic circulation without passing through the liver. Selective shunts theoretically decompress only part of the portal venous system while maintaining portal pressure and portal flow to the liver, even though late studies have revealed a loss of prograde flow to the liver. Devascularization procedures do not involve shunting of portal blood, but rather involve the devascularization of the stomach and esophagus that separates their venous drainage from the liver and portal system. Splenopneumopexy is an unusual but effective procedure for decompressing
patients with total mesenteric venous occlusion via the pulmonary veins. Liver transplantation is now more commonly used for treating patients with portal hypertension.

**Nonselective Shunts.** Nonselective shunts can be divided into total shunts or partial shunts. Examples of total nonselective shunts include the end-to-side portacaval shunt, large side-to-side portacaval shunt (>10 mm), mesocaval shunts, and central splenorenal shunts. The end-to-side portacaval shunt is performed by dividing the PV in the porta hepatis and performing an end-to-side anastomosis to the IVC with the proximal (splanchnic) end of the PV. This effectively decompresses the splanchnic bed and will nearly always control variceal hemorrhage because the portal pressure is markedly reduced. However, the obstructed sinusoids remain under high pressure, and ascites is not usually controlled. Depending on hepatic reserve, there is an increased risk of hepatic decompensation that manifests as worsening hepatic encephalopathy or even liver failure requiring liver transplantation. Patients with well-preserved synthetic function (eg, schistosomiasis) may tolerate and end-to-side shunt without complication.

A side-to-side portacaval shunt is performed by mobilizing a length of the PV (from the head of the pancreas to its bifurcation) and the IVC (from the inferior edge of the liver to the renal veins) and performing a side-to-side anastomosis (Fig. 61-12). In some cases a portion of the caudate lobe needs to be resected to allow a direct anastomosis between the PV and IVC, or a short interposition graft may be required. Because portal pressure is much greater than the central venous pressure in the vena cava and because there is greater resistance to flow through the cirrhotic liver, large side-to-side portacaval shunts are physiologically nearly equivalent to an end-to-side shunt, with effectively all the portal flow being diverted into the vena cava with reversal of flow (hepatofugal flow) to the liver and reduced portal venous perfusion. Although ascites can be effectively decreased by this method because the sinusoidal and splanchnic beds are both decompressed, encephalopathy is often heightened as a consequence and there is again a risk of liver failure. This can accelerate the need for liver transplantation. A side-to-side portacaval shunt is still the treatment of choice for patients with Budd–Chiari syndrome and if performed early enough after the diagnosis can lead to preservation of liver function and prevent the development of cirrhosis. Orloff’s series demonstrated 94% long-term survival with well-preserved
liver function and no ascites or encephalopathy.

FIGURE 61-12 Side-to-side portacaval shunt.

Mesocaval shunts are performed using an interposition graft (usually ribbed polytetrafluoroethylene [PTFE]) between the SMV and the IVC, and are associated with a high rate of thrombosis. The central splenorenal shunt is performed by dividing the distal SV, splenectomy, and performing an anastomosis between the SV and the left renal vein. Both these shunts are physiologically similar to an end-to-side portacaval shunt with hepatofugal flow and all the attendant risks.

Selective Shunts. Selective shunts are partially decompressive and include the Sarfeh mesocaval shunt (Fig. 61-13) and the distal splenorenal shunt (DSRS) (Figs 61-14 and 61-15). They are referred to as selective because they have the potential to preserve portal flow (Sarfeh and DSRS) and decompress the splanchnic beds separately, such as the gastroesophageal
network in the case of the DSRS. The Sarfeh shunt is a side-to-side shunt from the SMV to the IVC that can maintain forward portal flow, but also decreases portal pressure via small, 8 mm Dacron or PTFE grafts (Fig. 61-13). Since it is prosthetic, it does not expand like side-to-side portacaval shunts can, which can lead to them becoming complete shunts. This does not involve portal dissection and can thus render less complicated a subsequent transplant. It also has a lower rate of postoperative encephalopathy while providing improved ascites control and variceal decompression.\textsuperscript{53}

\textbf{FIGURE 61-13} Sarfeh mesocaval shunt.
FIGURE 61-14  Distal splenorenal shunt demonstrating an anastomosis between the mobilized splenic vein and the left renal vein. The splenic vein is oversewn at the junction with the superior mesenteric/portal vein confluence.
The distal splenorenal shunt venous flow from the splenic vein through the renal vein into the inferior vena cava thus bypassing venous blood flow away from the portal vein.

The DSRS was developed by Dean Warren in 1967 as a means of achieving selective gastroesophageal variceal decompression and preservation of portal flow, thus mitigating the risk of postoperative hepatic decompensation. It is performed by mobilizing the SV along the inferior border of the pancreas and disconnecting all the small branches to the pancreas, preserving the spleen, performing an anastomosis between the SV and the left renal vein, and dividing other collaterals between the PV and the shunt including the coronary (left gastric) vein (Figs 61-14 through 61-17). Benefits include control of variceal hemorrhage in 94% of patients, avoidance of portal dissection, maintenance of antegrade portal flow in 90% of patients, and a lower incidence (15%) of hepatic encephalopathy. Durable variceal decompression, however, comes at the cost of increased ascites. The “ascitogenic” nature of the operation originates from the extensive retropancreatic dissection required to mobilize the distal SV from the
pancreas in order to perform the anastomosis to the left renal vein. Another important consideration is the need to perform a splenopancreatic disconnection by discrete ligation and division of numerous SV branches. If not divided, they can enlarge in the months to years that follow and lead to hepatofugal flow and loss of selectivity of the shunt, particularly in patients with alcoholic liver disease. This disconnection, however, further heightens the risk of ascites. As such, DSRS is relatively contraindicated in patients with medically refractory ascites.

FIGURE 61-16 Intraoperative photo of anastomosis (arrow) of splenic vein (SV) to the left renal vein (RV).
Devascularization. Devascularization is an approach to portal hypertensive varices that involves direct surgical ligation of esophageal veins, short gastric veins, the lesser and greater curve veins of the stomach. It preserves hepatopetal flow. Sugiura in 1973 championed this approach and added to the above components esophageal transection and anastomosis and splenectomy.\(^{56}\) He reported rebleeding rates as low as 2\% in Japan and a 7-year survival rate of 83\%, but in other countries the bleeding rate ranges from 10\% to 54\% and survival is lower.\(^{57}\) It may be best reserved as a last resort in the case of endoscopically refractory variceal hemorrhage and extensive portal and mesenteric venous thrombosis, when other approaches are not available. Others have achieved better results with a 10\% incidence of rebleeding.\(^{58}\) Jin and Rikkers described a modified Sugiura procedure performed only transabdominally with division of the esophageal plexus up to the level of the inferior pulmonary ligament through the hiatus and splenectomy without division of the esophagus, along with a selective
vagotomy and pyloroplasty with good results in selected patients\textsuperscript{59} (Fig. 61-18). It is important that the left gastric vein (coronary vein) and paraesophageal collateral veins are preserved so that collaterals between the portal and azygous systems can develop and thereby reduce the chance of reformation of varices.

\textbf{FIGURE 61-18} Modified Sugiura devascularization procedure for total mesenteric venous thrombosis.

\textbf{Splenopneumopexy.} Splenopneumopexy is designed to lead to collateral circulation between the portal system and the pulmonary veins\textsuperscript{60}. An anastomosis between the parenchyma of the transected superior pole of the spleen and the left lower lobe of the lung after removal of the pleura from the lung surface is performed through the left hemidiaphragm. Preoperative
splenic artery embolization is usually performed. This procedure is most commonly applied in patients with total mesenteric venous occlusion and is an alternative to devascularization procedures (Fig. 61-19).

FIGURE 61-19 Splenopneumopexy for total mesenteric venous thrombosis.

**Liver Transplantation.** Liver transplantation is now frequently used to treat patients with advanced cirrhosis and complications of their cirrhosis including portal hypertension, as outcomes have improved.\(^56\) Patient selection and evaluation are key aspects of the care of cirrhotic patients. The most common disease indications for liver transplantation include acute liver failure (1%), hepatitis C virus (HCV) (29%), alcoholic liver disease (25%), cholestatic disease including nonalcoholic steatohepatitis (8%), malignancy (8%), and other/unknown (29%). However, it is usually the complications of cirrhosis and portal hypertension that lead to liver transplantation, some of which have been discussed above (eg, ascites, hepatic hydrothorax, gastric and esophageal varices and hemorrhage, hyponatremia, malnutrition, jaundice, hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy). Patient selection requires careful attention to the risk:benefit and outcomes of medical or surgical management of their disease versus liver transplantation. This is greatly informed by the MELD score, which predicts mortality on the waiting
list. Patient selection must consider other medical and surgical comorbidities and risk factors, psychosocial factors (particularly for those with a drug or alcohol problem in the past), and technical factors. Once a patient is on the waiting list, organs are prioritized and allocated by MELD scores, with the sickest patients with the highest MELD score being transplanted first. The outcomes of liver transplantation have continued to improve with 1-, 3-, and 5-year patient survival being 86%, 78%, and 70%, respectively.\textsuperscript{61}

**RADIOLOGIC MANAGEMENT**

**Transjugular Intrahepatic Portosystemic Shunt.** TIPS was developed by Josef Rosch in 1969 in a canine model in which an intrahepatic channel was created radiologically between the hepatic vein (HV) and PV in order to reduce portal pressure. In 1982, TIPS was first used clinically by Ronald Colapinto. In the mid-1980s, Julio Palmaz was the first to use a stent in a canine model in order to improve patency. In 1988, the first TIPS with stenting in a human was performed by Goetz Richter. PTFE-covered stents have been adopted during the last decade, resulting in marked improvement in long-term shunt patency.

**Indications.** TIPS is most commonly indicated in bleeding patients in whom endoscopic and pharmacological therapy have failed or in patients with recurrent bleeding after EVL (Table 61-7). A randomized control trial by Garcia-Pagan et al.\textsuperscript{62} concluded that the early use of TIPS in patients with acute variceal bleeding led to a significant reductions in both treatment failure and mortality. It is frequently used as a bridge to transplantation in patients with advanced liver disease and severe PHTN. As with any procedure, balancing the risks and benefits is important in these critically ill patients who are at risk for progressive liver failure and death. The MELD score was introduced and uses the patient’s serum bilirubin, serum creatinine, and the international normalized ration (INR) for prothrombin time to predict survival after TIPS according to the following formula:

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**TABLE 61-7: INDICATIONS FOR TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)**
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Refractory acute variceal bleeding (gastric or esophageal)
Secondary prevention of variceal bleeding (gastric or esophageal)
Portal hypertensive gastropathy
Refractory ascites
Hepatorenal syndrome
Hepatic hydrothorax
Budd-Chiari syndrome
Hepatic venoocclusive disease
Hepatopulmonary syndrome

MELD = 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dL)] + 6.43

The MELD score was found to be superior to the CTP score at predicting post TIPS mortality. The 3-month mortality for a patient undergoing a TIPS with a MELD score of 40 or more is 71.3%, 30 to 39 is 52.6%, 20 to 29 is 19.6%, 10 to 19 is 6.0%, and <9 is 1.9% (Table 61-5).

Relative contraindications include hepatic encephalopathy, congestive heart failure, tricuspid regurgitation, cardiomyopathy, pulmonary hypertension, and renal vein (RV) diastolic dysfunction (Table 61-8).

### TABLE 61-8: CONTRAINDICATIONS FOR TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)

**Absolute**
Primary prevention of variceal bleeding
Congestive heart failure
Multiple hepatic cysts
Uncontrolled systemic infection or sepsis
Unrelieved biliary obstruction
Severe pulmonary hypertension (mean pulmonary artery pressure >45 mm Hg)
Severe tricuspid regurgitation

**Relative**
HCC especially if central
Obstruction of all hepatic veins
Portal vein thrombosis
Severe coagulopathy (INR >5)
Thrombocytopenia of <20,000/cm$^3$
Right ventricular diastolic dysfunction
Moderate pulmonary hypertension
Hepatic encephalopathy

**Procedure.** Cross-sectional imaging of the abdomen should be obtained in all patients undergoing TIPS to define the hepatic vascular anatomy and patency of the PV, identify any anatomic variants that could influence the ability to perform the procedure, and to assess for evidence of malignancy.

There are three main HVs: the right (RHV), middle (MHV), and left (LHV). All usually enter the inferior vena cava (IVC) within 2 cm of the right atrium (RA). In most cases, the MHV and LHV form a common trunk and enter the IVC anteriorly while the RHV enters the IVC posterolaterally and more cephalad. HV size and morphology are variable and can be dramatically altered by cirrhosis. Anomalous HV and PV anatomy are seen in up to 30% of patients. In 3% to 5% of patients, a large inferior RHV may drain directly to the IVC well below the level of the RA. In this situation, the superior RHV may be atretic or absent. Occasionally, none of the HVs are accessible (such as in Budd–Chiari syndrome) and a direct IVC-to-PV-shunt (DIPS) may be considered.

PV anatomic variants are common as well. In 90% of patients, a right portal vein (RPV) trunk is present, bifurcating into anterior and posterior branches. The trunk is located between the 10th and 12th ribs approximately 0.5 to 1.5 vertebral widths to the right of the lateral margin of the spine. This information is important when using landmarks to target the PV. In 11% of patients, there is no RPV trunk and instead there is a trifurcation of the main portal vein (MPV) into anterior and posterior RPV branches and the left portal vein (LPV). Other common variants include the right posterior segment coming directly from the MPV (5%) and the right anterior segment arising from the LPV (4%). The RHV separates the anterior and posterior segments of the right hepatic lobe, originating cephalad and posterior to the RPV trunk. The MHV separates the right and left hepatic lobes and originates cephalad and anterior to the RPV.  

\[^{64}\]
Most interventional radiologists prefer to create the shunt from an RHV approach. The right internal jugular (IJ) is accessed, and right atrial, free hepatic, and wedged hepatic venous pressures are measured. A suitable branch of the right hepatic vein is then cannulated (Fig. 61-20A). Using a balloon occlusion catheter or end-hole catheter, wedged hepatic venography is performed with either dilute contrast or carbon dioxide (CO₂) to gently opacify the hepatic sinusoids and ultimately the PV in a retrograde fashion, allowing for direct visualization of the PV (Fig. 61-20B). CO₂ is preferred because of its low viscosity, low cost, lack of toxicity, and free reflux across the sinusoids, resulting in excellent filling of the PV.⁶⁴
FIGURE 61-20 Images from a 54-year-old man with recurrent esophageal variceal bleeding despite maximal endoscopic banding and medical management caused by hepatitis C cirrhosis. A. Right hepatic venogram demonstrates patency and course of the vein (arrow) as well as location of the hepatic vein/IVC junction (arrowhead). B. A wedge hepatic venogram using carbon dioxide shows the course and location of the portal veins. C. Iodinated contrast venogram after successful cannulation of the right portal vein through the TIPS cannula before portal passage of the guidewire. D. Simultaneous portovenogram and hepatic venogram using a marker pigtail catheter allow for accurate measurement of the TIPS shunt (portosystemic gradient, 22 mm Hg). Notice hepatofugal flow in the inferior mesenteric vein (arrow) as well as filling of esophageal varices via the coronary (arrowhead) and posterior gastric veins (*). E. Portogram obtained after TIPS insertion shows flow through the polytetrafluoroethylene-covered (PTFE) Viatorr stent (WL Gore, Flagstaff, AZ). The peripheral portal branches no longer fill due to reversal of flow; however, the coronary and posterior gastric veins persist supplying the esophageal varices. F. Completion portovenogram following successful coil occlusion of the coronary and posterior gastric veins. The portosystemic gradient fell to 8 mm Hg.

Once the location of the PV is known, needle passes are made from the HV through the hepatic parenchyma under fluoroscopic guidance. The needle is slowly withdrawn with gentle aspiration using a contrast-filled syringe. Brisk blood return into the aspiration syringe signals access into a vascular
structure, ideally the PV. Injection of a small volume of contrast material fluoroscopically confirms appropriate positioning in the PV (Fig. 61-20C).

A guidewire is then passed through the access needle into the PV and ultimately manipulated into either the SV or SMV and exchanged for a catheter to directly measure portal pressures that are compared to the right atrial pressure to establish the pre-shunt PSPG. Digital subtraction angiography is then performed outlining the portal and hepatic venous systems and the presence and location of portosystemic collaterals (Fig. 61-20D). The length of the parenchymal tract is measured from the PV access site to the HV/IVC confluence. The outflow of the stent should be within 1 cm of the of the HV/IVC confluence to reduce shunt outflow stenosis. Usually 1 cm is added to the measurement to account for the arc of the tissue track once the stiff wire is removed.

Catheterization of the PV with the 10 Fr TIPS sheath is necessary to facilitate placement of the PTFE-covered stent graft. The tissue track is predilated to the intended diameter of the shunt and to ease the advancement of the TIPS sheath. The sheath must be advanced several centimeters into the MPV beyond the PV access to ensure placement of the uncovered caudal portion of the stent in the PV. The covered portion of the stent is placed across the parenchymal track to the HV/IVC confluence. The covered portion was devised to reduce bile contact from crossed biliary radicles and reduce pseudointimal hyperplasia, the leading cause of in-stent stenosis and thrombosis in TIPS performed with bare metal stents. A 10- or 12-mm stent diameter is typically chosen for adults, while 8-mm stents are typically used in the pediatric population.

Once the stent is deployed, it is molded using the same balloon that was used for the initial track dilation, usually an 8-mm balloon. If a 10- or 12-mm stent was placed, this allows additional dilation if the post-TIPS gradient has not been sufficiently reduced.

Following placement of the shunt, post-TIPS pressures are measured. A post-TIPS PSPG of <12 mm Hg in patients with a history of variceal bleeding should be achieved to prevent further bleeding episodes. Following pressure measurements, the pigtail catheter is repositioned in the PV and a repeat portogram is performed from the same position as the original with the same injection rate to assess flow though the shunt as well as to evaluate persistent filling of portosystemic collaterals (Fig. 61-20E).
Outcomes. Success rates with TIPS for decompression of the portal system are >90% of cases in most series. SIR consensus guidelines state that a technically successful outcome that includes both creation of the shunt and a decrease in portal pressure to <12 mm Hg should be achieved in 95% of patients, and clinical success (resolution of the complication of portal hypertension) should be achieved in 90% of cases.66

A longitudinal pharmacological study demonstrated the risk of bleeding was zero when the HVPG was lowered to ≤12 mm Hg. Subsequent studies have shown that an overall reduction of the HVPG of >20% confers a significant reduction in the risk of bleeding.67 Therefore, a reduction in the HVPG >20% or an absolute value <12 mm Hg are the accepted therapeutic targets of therapy.68

Numerous randomized controlled trials as well as two recent meta-analyses found more than a threefold decrease in the risk of recurrent bleeding after TIPS placement compared with endoscopic therapy with similar all-cause mortality rates. Rebleeding after TIPS ranged from 9% to 40.6% compared to 20.5% to 60.65 with endoscopic therapy. There was a more than twofold increase in the rate of development of hepatic encephalopathy after TIPS, but hepatic encephalopathy can usually be easily controlled with medical therapy.69

TIPS is now the most widely used method for decompressing PHTN in patients with variceal bleeding who have failed EVL, replacing most surgical shunts, and is often used in patients with intractable ascites and hepatic hydrothorax.

Embolization of Varices Post-TIPS. A recent case control study suggested that even patients with target PSPGs following TIPS placement for variceal bleeding can benefit from variceal embolization.70 Coil embolization is the most widely used method to occlude varices and should be performed post TIPS in patients with recent variceal hemorrhage even when a target PSPG is achieved (Fig. 61-20F).

PTFE-Covered Stents. The development of PTFE-covered stent grafts has significantly reduced the occurrence of TIPS dysfunction, according to two large studies. The first series included 71 patients in a nonrandomized, non-controlled study. In those enrolled, eight shunt revisions were performed for an incidence of 11.3%. Primary patency rates at 6 and 12 months were 87%
The second was a randomized controlled trial comparing bare metal stents with PTFE stent-graft. Eighty patients with cirrhosis and either refractory ascites or recurrent variceal bleeding were enrolled. Patients were followed with Doppler US and venography was performed at 6, 12, and 24 months post-TIPS. Only 13% of the patients receiving stent grafts had shunt dysfunction, whereas 44% of those receiving bare stents had dysfunction. Also, early thrombosis was seen in three patients receiving bare metal stents. The actuarial rates of primary patency in the covered and bare metal stent groups were 86% and 47%, respectively at 1 year, and 80% and 19% at 2 years. On the basis of this data, PTFE-covered stents have become the standard of care device for de novo TIPS, and patients who have bare metal stents and need repeat intervention should undergo shunt revision with a PTFE-covered stent graft.

**TIPS Maintenance.** A baseline Doppler US is performed 1 to 4 weeks following TIPS placement and usually every 3 to 6 months thereafter. Immediate US is hampered by microbubbles retained in the PTFE-covered stent grafts. Shunt velocities of 250 cm/s or greater or 50 cm/s or less are associated with high sensitivity (>90%) and specificity for shunt dysfunction. The best indicator of TIPS dysfunction is recurrence of the clinical symptoms for which the shunt was originally placed and should prompt a Doppler US for evaluation.

Patients suspected of TIPS dysfunction should undergo TIPS venography. If the original TIPS was created with a bare metal stent, it should be covered with a PTFE-covered stent graft. Other commonly used interventions include balloon angioplasty for stenosis or stent extension for shunts that are too short either cranially or caudally.

**Complications (Table 61-9).** TIPS dysfunction is defined as ≥50% stenosis of the shunt, an increase in the HVPG to >12 mm Hg, or recurrence of the problem for which the shunt was placed (eg, bleeding varices) and is usually caused by pseudointimal hyperplasia within the stent. As discussed above, 13% of the patients receiving covered stent grafts had shunt dysfunction over 2 years, compared to 44% in those with bare metal stents. Close monitoring with Duplex US is important for long-term patency, and if shunt dysfunction is suspected hepatic venography should be performed. Shunt thrombosis typically occurs in 10% to 15% of patients with bare metal stents within 24
hours of placement.\textsuperscript{37,73} If early shunt thrombosis is suspected, CT or MR venography can be performed to assess shunt dysfunction.

<table>
<thead>
<tr>
<th>TABLE 61-9: TIPS COMPLICATIONS</th>
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<tr>
<td>TIPS dysfunction</td>
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<tr>
<td>Bare metal</td>
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<tr>
<td>Covered</td>
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<tr>
<td>Transcapsular puncture</td>
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<td>Intraperitoneal bleed</td>
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<tr>
<td>Hepatic infarction</td>
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<td>Fistulae</td>
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<td>Hemobilia</td>
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<td>Sepsis</td>
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<tr>
<td>Infection of TIPS</td>
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<tr>
<td>Hemolysis</td>
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<td>Encephalopathy</td>
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<tr>
<td>New/worse</td>
</tr>
<tr>
<td>Chronic</td>
</tr>
<tr>
<td>Stent migration or placement</td>
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<td>into IVC or too far into PV</td>
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The incidence of new or worsening encephalopathy following TIPS is 20\% to 31\%. Pre-TIPS factors associated with an increased risk of encephalopathy include etiology of liver disease other than alcohol, female gender, and hypoalbuminemia as well as increasing age, past history of encephalopathy, and evidence of encephalopathy at the time of TIPS. Only if hepatic encephalopathy is uncontrolled is TIPS contraindicated. In most cases, encephalopathy responds well to standard therapies, and only rarely (~5\%) does the TIPS need to be occluded to control the encephalopathy.\textsuperscript{37,69}

The incidence of fatal complications (intra-abdominal hemorrhage, laceration of the HA or PV, and right heart failure) is less than 1.5\%. Technical complications include transcapsular puncture in up to 33\% of cases, although capsular perforation leads to significant hemorrhage in only 1\% to 2\% of cases. Clinically significant hemobilia is rarely seen. The stent
can be placed too far cranially into the IVC or RA or too deep caudally into the PV in up to 20% of cases. The stent outflow should be placed to the junction of the HV and the IVC. Stents that are left short will ultimately lead to stenosis at the stent/hepatic vein interface and TIPS dysfunction, and should be extended at the time of initial placement.

**Direct Intrahepatic Portacaval Shunt.** DIPS is a modification of the TIPS procedure. It consists of direct access of the PV from the IVC via the caudate lobe, typically using intravascular US guidance. Once portal access is obtained, the shunt is created using a PTFE-covered stent graft in a similar fashion as a standard TIPS access. Physiologically this shunt is a side-to-side portacaval shunt from the IVC to the MPV through the caudate lobe of the liver. The DIPS procedure can be extremely helpful in patients with challenging anatomy, such as Budd–Chiari syndrome, patients with PVT, or hepatocellular carcinoma. In the right hands, DIPS may have added benefits over the standard TIPS technique including decreased fluoroscopy times, increased patency, and to extend the spectrum of patients with portal hypertension for whom endovascular portosystemic shunting can be performed.

**Balloon-Occluded Retrograde Transvenous Occlusion.** BRTO of gastric varices is an emerging technique that can be performed as an adjunct or alternative to TIPS for the management of isolated gastric varices. BRTO is indicated in patients who are not candidates for TIPS because of coagulopathy, high MELD score, or severe hepatic encephalopathy, as well as for the prophylaxis of high-risk gastric varices.

BRTO is performed by accessing the portosystemic gastrorenal shunt via the left renal vein from either a transfemoral or transjugular vein approach. A balloon catheter is advanced into the outflow shunt, inflated, and a retrograde digital subtraction venogram is performed to identify the gastric varices, their inflow and outflow vessels, and collaterals (Fig. 61-21A). Gastric collateral vessels can be occluded first with coils, glue, or gelatin sponge particles to decrease non-target embolization (Fig. 61-21B). The gastric varix can then be embolized under fluoroscopic control in a retrograde fashion either through the occlusion balloon catheter or through a microcatheter placed within the gastric varix (Fig. 61-21C). A foamed mixture of 3% sodium tetradecyl sulfate (STS) is used as the sclerosant. The endpoint of embolization is
minimal filling of the feeding portal branch (Fig. 61-21D). In addition, cone beam CT (performed on the angiography table) can be a valuable adjunct to the procedure to document complete filling of the varix. The balloon is left in place inflated for 4 hours post embolization to allow stabilization of the thrombus within the varix, and is removed under fluoroscopic guidance.79
55-year-old male with HCV cirrhosis and high-risk gastric varices presenting for balloon-occluded retrograde transvenous obliteration of gastric varices (BRTO). **A.** Retrograde venogram via the gastrorenal shunt
shows partial filling of the gastric varix (arrowhead) as well as collateral systemic outflow through the inferior phrenic vein (arrow). B. Successful coil occlusion of the inferior phrenic vein outflow. C. Retrograde venogram shows occlusion balloon (arrowhead) in the proximal gastrorenal shunt, with filling of the gastric variceal complex (arrows). D. Fluoroscopic image after administration of the sclerosant mixture with complete filling of the gastric variceal complex (arrows), the end point of embolization is minimal filling of the afferent portal branch (arrowhead).

Technical success, defined as successful filling of gastric varices with sclerosant, is reported to occur in 77% to 100% of cases. Complete obliteration of the gastric varices is reported in 82% to 100% of patients (Fig. 61-22A, B). In some studies, repeat BRTO is necessary to achieve these outcomes. Rebleeding rates are reported as high as 15%, but are typically much lower, with most studies showing rebleeding rates lower than 5%.77,78
FIGURE 61-22 55-year-old male with HCV cirrhosis and high risk gastric varices. A. Axial contrast-enhanced CT prior to BRTO demonstrates high-risk gastric varices (arrows). B. Axial contrast-enhanced CT 1 year after BRTO demonstrates complete obliteration of the previously seen varices (arrows).

Complications are uncommon but can include epigastric and back pain, fever and hematuria, bacterial peritonitis, worsening ascites and hydrothorax, PV and renal vein thrombosis, pulmonary embolism, ventricular fibrillation, pulmonary edema, and anaphylaxis to ethanolamine oleate. Another complication of BRTO is the aggravation of nongastric (esophageal or duodenal) varices caused by an increase in portal pressure after occlusion of a large gastrorenal shunt. Therefore, follow-up endoscopy is necessary after the procedure. Studies have shown an increase in esophageal varices at 1, 2, and 3 years of 27% to 35%, 45% to 66%, and 45% to 91%, respectively. Typically these varices can be managed endoscopically.

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy refers to changes in the gastric mucosa including friability, dilatation of the venules, and capillaries that have a characteristic mosaic or “snakeskin” appearance. Portal hypertensive gastropathy is often associated with bleeding, which can be slow chronic blood loss requiring intermittent transfusion or can be massive hemorrhage. β-blockade and octreotide have been used along with endoscopic therapy with fibrin or argon beam coagulation. TIPS is the most effective in controlling bleeding from portal hypertensive gastropathy.

Portal Vein Thrombosis and Total Mesenteric Venous Occlusion

PVT causes presinusoidal portal hypertension, may involve the intrahepatic branches, and may extend to involve the superior mesenteric or splenic veins. The prevalence of chronic PVT in cirrhotic patients is 10% to 25% and is even more common in patients with decompensated cirrhosis and a history of splenectomy.
As portal hypertension progresses, portal flow can become stagnant to the point of thrombosis. This can of course become complete and thus exacerbate ascites and variceal bleeding. It can also occur slowly over time. In this case it is often not associated with any identifiable perturbation in liver function or symptoms. However, newly diagnosed PVT in a cirrhotic mandates an assessment for hepatocellular carcinoma. About 25% of PVT is related to an underlying hepatocellular carcinoma or pancreatic carcinoma. Although it may be worth considering anticoagulation in the case of cirrhotic patients with partial PVT, these patients often have varices, and anticoagulation should not precede adequate bleeding prophylaxis and management.

In symptomatic patients with acute PVT, the choice of treatment is determined by the severity of the symptoms. Anticoagulation should be started immediately unless otherwise contraindicated. Bowel ischemia and infarction from total mesenteric venous occlusion necessitate surgical resection, but ischemia may respond to percutaneous therapies, and thrombolysis can be considered.

A number of case reports describe approaches to the treatment of portal and mesenteric venous thrombosis. The portal venous system can be accessed directly from transjugular, trans-hepatic, or trans-splenic routes, or indirectly via a transarterial approach for catheter-directed thrombolysis. A transjugular approach may be most appropriate in patients with preexisting cirrhosis when a TIPS is needed to decompress the portal system. The transjugular approach has additional advantages in patients with severe coagulopathy and massive ascites, whereas transhepatic or trans-splenic approaches pose a high risk of bleeding.

With these direct approaches the portal venous system is accessed, a multiside hole infusion catheter is placed across the thrombus, and thrombolytic therapy is initiated while the patient is monitored for signs of bleeding in the intensive care unit. Agents used include rTPA, urokinase, and streptokinase. In the transarterial (indirect) approach, a catheter is directed into the superior mesenteric artery, and thrombolytic infusion is delivered to the portal venous system across the capillary bed. Thrombolytic therapy is continued until either the thrombus resolves or there is no further improvement in the appearance of the thrombus, worsening clinical symptoms, evidence of systemic fibrinolysis, or bleeding complication.

In addition, catheter-directed mechanical thrombectomy (MT) can be
performed concomitantly to hasten clot removal. A commonly used device is the AngioJet, which is an over-the-wire device that can be easily manipulated through the thrombosed PV segment and utilizes a complex mixture of rapid fluid streaming and hydrodynamic forces to fracture thrombus, allowing extraction at the catheter tip using negative pressure (Bernoulli/Venturi principle). The catheter can also be used in “power pulse spray” mode to deliver a bolus dose of the thrombolytic of choice through the extent of the thrombus prior to MT. Other alternative techniques for clot removal have been described and include balloon embolectomy, suction catheter embolectomy, and basket extraction of thrombus. Following thrombus removal, it is necessary to identify the presence of an underlying “fixed” stenosis in the PV that can be corrected with balloon angioplasty and stent placement.

**Hepatic Encephalopathy**

Hepatic encephalopathy is a one of the most frequent and debilitating aspects of cirrhosis and PHTN. The cognitive impairment can be manifest in various neurologic or psychiatric abnormalities from subclinical disease to coma. These abnormalities can include extrapyramidal dysfunction, asterixis, myelopathy, apathy, and disinhibition. Poor synthetic function and TIPS or surgical portosystemic shunting for PHTN are the main etiologies in the cirrhotic patient. The prevalence of overt encephalopathy in decompensated cirrhosis is 16% to 21%, and post-TIPS 10% to 50%. Lactulose is the initial treatment strategy and is titrated to effect to achieve two to three bowel movements per day. Among other effects, it creates an acidic prebiotic colonic milieu that favors growth of beneficial microorganisms. This is thought to be the reason that laxatives alone are not effective treatments for overt encephalopathy. Rifaximin has been shown in clinical trials to be well tolerated and equivalent or superior in effect. It is often coupled with lactulose for overt encephalopathy refractory to lactulose alone. Although neomycin and metronidazole have been used for short-term therapy, they are not ideal as a part of chronic management due to morbidities including ototoxicity, nephrotoxicity, and neurotoxicity.

**Hepatorenal Syndrome**
Hepatorenal syndrome is characterized by a progressive rise in serum creatinine, normal urine sediment in most cases, absence of proteinuria (<500 mg per day), low rate of sodium excretion (urine sodium concentration <10 meq/L), and oliguria in patients with severe liver disease, and is a diagnosis of exclusion. There are two forms: Type 1 hepatorenal syndrome, defined as at least a twofold increase in serum creatinine to >2.5 mg/dL over less than 2 weeks, and Type 2, defined as renal dysfunction that is less severe than Type 1 and is often associated with diuretic resistant ascites. The ideal therapy is recovery of liver function. Other treatments include volume expansion, norepinephrine (or vasopressin) in combination with albumin, terlipressin plus albumin, or midodrine, octreotide, and albumin if terlipressin is not available, TIPS, dialysis, and ultimately liver transplantation. Most patients with hepatorenal syndrome die within weeks without therapy. Patients can be maintained on dialysis, but usually die of their liver disease without transplantation. After successful liver transplantation, renal function recovers with the restoration of normal liver function.

**Hepatopulmonary Syndrome**

Hepatopulmonary syndrome (HPS) is manifest as a defect in oxygenation associated with pulmonary vascular dilatation and arteriovenous communications that occur in patients with liver disease. The clinical manifestations usually occur only after many years of liver disease and include dyspnea on exertion, at rest, or both, digital clubbing, facial telangiectasia, wheezing, and syncope. Patients with chronic liver disease should have screening pulse oximetry and if it is less than 97% on room air in a standing or sitting position, further evaluation should be performed including an arterial blood gas. The prevalence of HPS in cirrhotic patients is between 15% and 20%. The best next test (chest radiograph is usually normal) is a contrast-enhanced transthoracic echocardiogram, which should be performed with saline that has been shaken to produce microbubbles and is then injected into a peripheral vein in the arm. Microbubbles (>10 µm in diameter) do not pass through normal capillaries (<8 to 15 µm in diameter), so the detection of microbubbles in the left atrium within three to six cardiac cycles indicates their passage through dilated pulmonary capillaries or through arteriovenous communications. An intracardiac shunt can also give a positive bubble echo result. Only pulmonary angiography can tell the
difference between the first two entities, and transesophageal contrast-enhanced echocardiography can detect intracardiac shunts. A 99m Tc Technetium-macroaggregated (MAA) perfusion lung scan can be used to quantify and follow the degree of intrapulmonary shunting (27.8% highly specific for intrapulmonary shunting with hypoxia).

It is important to determine the severity of the HPS because it determines survival and aids in determining the timing for liver transplantation. The degree of severity is defined by an alveolar-arterial oxygen gradient ≥15 mm Hg and \( P_{a}O_{2} ≥80 \) mm Hg (mild), ≥60 to <80 mm Hg (moderate), ≥50 to <60 mm Hg (severe), and <50 mm Hg (very severe). The median survival of patients who are not candidates for liver transplantation is 24 months, with a 5-year survival of 23%; survival is significantly worse for patients with a \( P_{a}O_{2} <50 \) mm Hg.

There are no effective medical treatments for HPS and the only option is liver transplantation. Patients should be treated with supplemental \( O_{2} \) to relieve symptoms. The indications for liver transplantation are a \( P_{a}O_{2} <60 \) mm Hg on RA while sitting and a positive bubble echo. Patients are given priority on the waiting list by the granting of HPS MELD exception points. A recent review of patients transplanted for HPS showed that there was no association between pre-transplantation \( P_{a}O_{2} \) and waitlist survival, but a pretransplant \( P_{a}O_{2} ≤44 \) mm Hg was associated with an increased mortality post-transplant compared to patient with a \( P_{a}O_{2} \) 44.1 to 54.0 mm Hg (hazard ratio = 1.58).

**Portopulmonary Hypertension**

Portopulmonary hypertension (POPH) is often confused with hepatopulmonary syndrome because the initial clinical manifestations are similar. POPH, however, can be associated with mild hypoxemia, but not with the severe hypoxemia seen with HPS. Its prevalence is thought to be about 8.5% in patients with liver disease and it is recommended that all patients should be screened for POPH by transthoracic echo. In portopulmonary hypertension, vasoconstriction of the pulmonary arterial bed leads to obstruction of flow. There is also endothelial and smooth muscle cell proliferation, in situ thrombosis, and arteriopathy. Chest radiograph and
EKG may reveal a prominent pulmonary artery and right ventricular hypertrophy, but both can be normal. An echocardiogram may show elevations in right ventricular systolic pressures (>50 mm Hg). The diagnosis should be confirmed by a right heart catheterization and measurement of pulmonary hemodynamics that show a mean pulmonary artery pressure >25 mm Hg, pulmonary vascular resistance >240 dyn·s/cm\(^5\), and a normal or decreased pulmonary capillary wedge pressure <15 mm Hg. Mild portopulmonary hypertension is defined by a mean PAP 25 to 35 mm Hg, moderate 35 to 45 mm Hg, and severe >45 mm Hg.

The treatment of POPH includes supplemental oxygen for hypoxemia (which can worsen POPH via vasoconstriction), prostanoids such as epoprostenol, combination therapy with endothelin receptor antagonists such as intravenous Iloprost and oral Bosentan, and phosphodiesterase inhibitors such as sildenafil.\(^{94}\) The survival of untreated POPH is poor, and the aforementioned medical therapies are associated with improved survival rates.\(^{95}\) However, the best survival is with liver transplantation (67% at 5 years), although this depends on the severity of the POPH. For example, the mortality rate of liver transplantation is 35% in patients with a mean PAP >35 mm Hg. Medical therapy should first be implemented to bring the mean PAP down below 35 mm Hg before attempting a liver transplant to maximize outcomes.

**PORTAL HYPERTENSION IN CHILDREN**

The management of portal hypertension in children has changed just as it has in adults with improvements in outcomes related primarily to better medical therapy, better endoscopic and radiologic variceal control, and liver transplantation. Emergency shunts are rarely required and TIPS can be used as a bridge to transplant, although the experience in children is limited. It is important to note that the approach to children who have normal parenchyma and well-preserved synthetic function is different than for those with cirrhosis and hepatic dysfunction just as it is in adults.

An interesting aspect of the treatment of children with PHTN are patients with extrahepatic PVT, the management of which has changed significantly since the development of the mesenteric vein-to-LPV bypass for post-transplant PVT.\(^{96}\) The operation, referred to as a Rex shunt, involves
shunting blood from the patent but obstructed mesenteric vein to the still patent LPV (Fig. 61-23). The criteria for the procedure include no intrinsic liver disease, a patent intrahepatic portal venous system, and a suitable vein in the mesenteric venous system to provide inflow. The procedure is started by dissecting out the intrahepatic LPV in the recessus of Rex where the round ligament enters the liver between segments III and IVB. This requires some excision of liver parenchyma (segments III and IVB) and all the branches to segments II, III, and IV are ligated and divided. The SMV or alternatively the splenic, inferior mesenteric, or coronary veins are dissected out and prepared for anastomosis. The IJ vein is then removed and anastomosed to the intrahepatic PV and then to the SMV. The vein graft usually tracks through the transverse mesocolon and the lesser sac behind the stomach and to the liver. This shunt can restore portal flow to the liver and relieve the portal hypertension resulting from PVT. Patency rates exceed 90% in properly selected patients.

**FIGURE 61-23** Mesenteric-to-left portal vein bypass (Rex shunt) for extrahepatic portal vein thrombosis.

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GALLBLADDER AND BILE DUCTS
CHOLELITHIASIS AND CHOLECYSTITIS

Ezra N. Teitelbaum • Nathaniel J. Soper

HISTORY AND BACKGROUND

Cholecystectomy is one of the most common surgical procedures performed in the United States, with over 700,000 procedures performed each year. Open cholecystectomy, first performed by Carl Langenbuch in 1882, had been the primary treatment of gallbladder disease through the early 1990s. In 1985, the first endoscopic cholecystectomy was performed by Erich Mühe of Böblingen, Germany. Shortly thereafter, pioneers in France and the United States coupled a video camera with a laparoscope to allow the surgeon and the entire surgical team to more easily view the operative field and performed cholecystectomies with laparoscopic equipment. Since then, laparoscopic cholecystectomy has been adopted around the world, and subsequently been recognized as the gold standard for the treatment of gallstone disease. The first laparoscopic cholecystectomy in the United States was performed in 1988, and by 1992, the National Institutes of Health (NIH) Consensus Development Conference stated that laparoscopic cholecystectomy provides a safe and effective treatment for most patients with symptomatic gallstones.
Currently, it is estimated that approximately 90% of cholecystectomies in the United States are performed using a laparoscopic approach.\(^6\)

The advantages of laparoscopic over open cholecystectomy have been well documented. These advantages include earlier return of bowel function, less postoperative pain, improved cosmesis, shorter length of hospital stay, earlier return to full activity, decreased wound infections and incision hernia formation, and decreased overall cost.\(^4,5,7,8\) There has been an increase in the rate of cholecystectomies subsequent to the introduction of laparoscopic cholecystectomy accompanied by evidence of lower clinical thresholds for operative therapy of gallbladder disease.\(^9,10\)

**INDICATIONS FOR CHOLECYSTECTOMY**

**Symptomatic Cholelithiasis**

There are multiple indications for cholecystectomy, with the most common being symptomatic cholelithiasis, also termed “biliary colic” (Table 62-1). Biliary colic typically presents as a severe and episodic right upper abdominal or epigastric pain that can radiate to the back. Attacks frequently occur within 1 to 2 hours postprandially or awaken the patient from sleep. Most often, the postprandial pain will be associated with meals that are high in fat content. These episodes typically last between 30 minutes and 6 hours and can be associated with nausea and vomiting.

**TABLE 62-1: INDICATIONS FOR LAPAROSCOPIC CHOLECYSTECTOMY**

**Symptomatic cholelithiasis**  
Biliary colic  
Acute cholecystitis

**Choledocholithiasis**  
Obstructive jaundice or cholangitis  
Gallstone pancreatitis

**Asymptomatic cholelithiasis**
Sickle cell disease
Chronic immunosuppression
No immediate access to health care
Incidental cholecystectomy for patients undergoing intra-abdominal operations for other reasons

**Acalculous cholecystitis**
**Functional gallbladder disorder**
**Gallbladder polyps >10 mm**
**Porcelain gallbladder**

Once a patient begins to experience symptoms, there is a greater than 80% chance that he or she will continue to have symptoms in the future or develop a complication. These complications may result from obstruction of the gallbladder outlet, causing acute cholecystitis, or migration of a stone into the common bile duct, causing cholangitis or pancreatitis. Because there are no effective medical therapies for cholelithiasis, any patient who develops symptoms from gallstone disease should be offered laparoscopic cholecystectomy, given their medical comorbidities do not pose a prohibitive operative risk.

Patients being considered for laparoscopic cholecystectomy should undergo a complete medical history and physical examination. The history should focus on confirming that the patient’s symptoms are consistent with biliary colic and determining whether they have symptoms indicative of complications of gallstone disease, such as acute cholecystitis, choledocholithiasis, or gallstone pancreatitis. Additionally, a complete medical history is required to determine the patient’s overall surgical risk. Patients with symptomatic cholelithiasis do not typically manifest any signs on physical exam, even when they are in the midst of a pain episode. This is because their pain is visceral in nature, without associated inflammation that would cause local peritonitis and somatic pain. As a result, if a patient has significant right upper quadrant tenderness on exam, it should be suspected that they have acute cholecystitis or another inflammatory process.

Patients being evaluated for gallstone disease should have a complete metabolic panel, including liver function tests (LFTs), and a complete blood count (CBC). Elevations in the LFTs, especially direct bilirubin, may suggest biliary obstruction from choledocholithiasis. Elevations in amylase and, more
specifically, lipase may indicate gallstone pancreatitis. A leukocytosis is suggestive of acute cholecystitis.

In a patient with typical biliary colic, the only diagnostic imaging study necessary prior to laparoscopic cholecystectomy is an abdominal ultrasound revealing gallstones. Ultrasound demonstrates the size and number of stones, the thickness of the gallbladder wall, the presence or absence of pericholecystic fluid, the diameter of the common bile duct (CBD), and other components of the biliary ductal system. Gallstones are seen as rounded hyperechoic echoic shapes on ultrasound that cause hypoechoic “shadowing” deep to their location on the ultrasonic image (Fig. 62-1). Other nonbiliary disorders such as hepatic lesions or steatosis, masses in the pancreas, or renal tumors may also be diagnosed. If a patient with gallstones has atypical symptoms, however, a more extensive workup including upper gastrointestinal contrast radiography or endoscopy, computed tomography, or cardiac and pulmonary evaluation may be appropriate to rule out significant nonbiliary disease processes.

**FIGURE 62-1** Transabdominal ultrasound showing a gallstone within the gallbladder. The hyperechoic gallstone (GS) creates a hypoechoic “shadow”
Acute Cholecystitis

Acute cholecystitis occurs when a gallstone or sludge becomes lodged in the gallbladder-cyst duct junction, creating bile stasis in the gallbladder, which in turn leads to inflammation and infection. In contrast to biliary colic, patients with acute cholecystitis usually present to the emergency department with unrelenting right upper quadrant or epigastric pain, and can additionally have fevers and more severe nausea and vomiting. On physical exam, they can be febrile and tachycardic, but the most consistent exam finding is right upper quadrant tenderness, which is not typically present with biliary colic. Murphy sign is the traditional physical exam test for evaluating for acute cholecystitis. To elicit it, the examiner palpates the right upper quadrant immediately below the costal margin and asks the patient to inspire deeply. This maneuver moves the diaphragm inferiorly and brings the gallbladder into contact with the anterior abdominal wall under the examiner’s hand, which causes pain in the setting of cholecystitis. Thus, if the patient abruptly ceases inspiration due to pain, he or she is found to have a positive Murphy sign. A positive Murphy sign has been shown to have a sensitive of 97% and a specificity of 48% in diagnosing acute cholecystitis, with cholescintigraphy used as the “gold standard.”

Laboratory evaluation can reveal an elevated white blood cell count in patients with acute cholecystitis, although their liver function tests, especially the direct bilirubin, should be relatively normal given there is no biliary obstruction. Abdominal ultrasound should reveal the presence of gallstones and can additionally show 2 signs that are specific to cholecystitis: thickening of the gallbladder wall to greater than 4 mm and pericholecystic fluid. When combined, these findings have a sensitivity of 88% and specificity of 80% in diagnosing acute cholecystitis. However, in our experience, the presence or absence of these ultrasound findings does not correlate well with the degree of inflammation found at the time of subsequent operation.

A thorough history and physical examination, combined with findings on abdominal ultrasound, should be sufficient to confirm a diagnosis of acute cholecystitis in almost all instances; however, if doubt exists, cholescintigraphy (also known as a HIDA scan) can be used.
Cholescintigraphy is a nuclear medicine study in which a radiotracer, $^{99m}$Tc-hepatic iminodiacetic acid (HIDA), is injected intravenously and selectively taken up by the liver. The tracer is then excreted into the biliary tree, and a lack of uptake into the gallbladder signifies an obstruction of the cystic duct and thus a diagnosis of cholecystitis. Cholescintigraphy has a sensitivity of greater than 95% and a specificity of 90% in diagnosing acute cholecystitis.\(^{13}\)

Patients with acute cholecystitis should be admitted to the hospital, placed on bowel rest, volume resuscitated with isotonic intravenous fluid, and treated with intravenous antibiotics that cover gram-negative and anaerobic bacteria. Although some patients may improve with this conservative treatment, recurrence rates are high, and if the patients have acceptable operative risk, almost all patients with acute cholecystitis should undergo cholecystectomy for definitive treatment. This timing of this operation has long been a topic of considerable debate, with some advocating initial treatment with antibiotics and then performing a cholecystectomy on an elective basis several weeks later after the acute inflammation has abated. However, as more data have emerged during the laparoscopic era, it is becoming clear that a strategy of early cholecystectomy during the initial hospitalization for acute cholecystitis is safe and carries significant benefits. A randomized trial involving over 600 patients compared a strategy of early laparoscopic cholecystectomy (within 24 hours) with one of initial antibiotic therapy and interval cholecystectomy between 7 and 45 days later and found that the early surgery group had fewer complications (12% vs 34%), a shorter overall hospital length of stay, and lower hospital costs.\(^{14}\) A meta-analysis of 15 randomized controlled trials showed that early surgery for cholecystitis resulted in short hospital stays with lower costs and higher patient satisfaction and quality of life, while perioperative mortality and morbidity were similar between the early and delayed surgery groups.\(^{15}\)

Patients who are too high risk for surgery based on either their underlying medical comorbidities or sepsis due to severe cholecystitis can be treated with gallbladder decompression. This is generally done using a transabdominal cholecystostomy tube, placed under ultrasound or computed tomography (CT) guidance. Other options include endoscopic drainage with a transpapillary tube inserted during endoscopic retrograde cholangiopancreatography (ERCP) or a transduodenal tube inserted under endoscopic ultrasound (EUS) guidance. These drainage modalities are
generally effective in resolving the acute inflammatory process; however, they are temporary solutions, and if the tube is subsequently removed, patients are at a high risk of developing recurrent symptoms due to gallstones. For this reason, gallbladder decompression should be reserved for the sickest patients in whom early surgery would pose a prohibitive risk.

**Asymptomatic Cholelithiasis**

Patients with asymptomatic (ie, incidentally discovered) gallstones have a less than 20% chance of ever developing symptoms, and the risks associated with prophylactic operation outweigh the potential benefit of surgery in almost all patients. Prophylactic cholecystectomy for asymptomatic cholelithiasis can be justified in certain circumstances, such as in patients with sickle cell disease, those undergoing open bariatric surgery, those requiring long-term total parental nutrition, or possibly patients who are therapeutically immunosuppressed after solid organ transplantation. Patients with sickle cell disease often have hepatic or vaso-occlusive crises that can be difficult to differentiate from acute cholecystitis. In patients who have undergone bariatric surgery, the development of gallstones is markedly increased during the period of rapid weight loss, with an incidence of approximately 30%. Removing the gallbladder at the time of bariatric surgery can abolish gallstone-related morbidity relatively easily. This approach was adopted by many bariatric surgeons during open bariatric procedures, but this practice has largely been abandoned with the advent of laparoscopic bariatric surgery, because the potential morbidity of an added laparoscopic cholecystectomy in the patient with morbid obesity appears greater than the potential later risk of cholelithiasis-related complications.

In transplant patients, there is concern that immunosuppression may mask the signs and symptoms of inflammation until overwhelming infection has occurred. Recommendations in the literature range from mandatory screening and treatment of biliary disease before transplantation, to prophylactic cholecystectomy 6 months after transplantation, to expectant management of all asymptomatic patients. Other possible indications for prophylactic laparoscopic cholecystectomy include individuals who may not have access to modern health care facilities for an extended time period, such as missionaries and military personnel, and patients who are already
undergoing an abdominal operation for other reasons. Prophylactic cholecystectomy has been occasionally advocated in diabetics. There is no evidence to support this policy but good evidence to support a strategy of early cholecystectomy in the symptomatic patient. Diabetics tend to present with acute cholecystitis more frequently once they become symptomatic and withstand complications less well.

**Functional Gallbladder Disorder**

Functional gallbladder disorder (FGD) refers to patients who experience symptoms typical of biliary colic in the absence of gallstones and, in the past, has been referred to as gallbladder dyskinesia, biliary dyskinesia, gallbladder spasm, and/or acalculous biliary disease. The exact etiology of FGD is unknown, but it is thought to be a result of gallbladder dysmotility. FGD is often a diagnosis of exclusion, after evaluating for other common causes of upper abdominal and lower chest pain such as peptic ulcer disease, gastroesophageal reflux disease, pancreatitis, irritable bowel syndrome, musculoskeletal causes, and angina. Consensus guidelines developed by the Rome Committee have established criteria for the diagnosis of FGD.\(^{26}\) The most recent Rome III guidelines require that the patient’s pain must be located in the epigastrium and/or right upper quadrant and additionally meet all of the 8 criteria listed in Table 62-2. Additionally, patients must have normal LFTs and no gallstones on abdominal ultrasound. The strict list of inclusion criteria based on symptoms is meant to limit the number of cholecystectomies performed for FGD and increase the likelihood that such an operation will result in a resolution of said symptoms. The diagnosis of FGD is confirmed with cholecintigraphy. After the radiotracer is observed at maximal levels in the gallbladder, an infusion of cholecystokinin (CCK) is given to stimulate gallbladder contraction. The percentage of tracer ejected from the gallbladder in response to CCK is then measured, with an ejection fraction less than 35% to 40% being indicative of FGD. Patients with gallbladder ejection fractions below this threshold have markedly better symptomatic outcomes after cholecystectomy.\(^{27}\) According to the Rome III consensus, patients with an ejection fraction greater than 40% should be more carefully evaluated for alternative etiologies of their pain.
TABLE 62-2: CRITERIA FOR FUNCTIONAL GALLBLADDER DISORDER UNDER THE ROME III GUIDELINES

Episodes of pain must be located in the epigastrium and/or right upper quadrant and meet all of the following:
1. Episodes lasting 30 minutes or longer
2. Recurrent symptoms occurring at different intervals (not daily)
3. The pain builds up to a steady level
4. The pain is moderate to severe enough to interrupt the patient’s daily activities or lead to an emergency department visit
5. The pain is not relieved by bowel movements
6. The pain is not relieved by postural change
7. The pain is not relieved by antacids
8. Exclusion of other structural disease that would explain the symptoms

Gallbladder Polyps and Porcelain Gallbladder

Other indications for cholecystectomy include the radiographic findings of gallbladder polyps and porcelain gallbladder. Gallbladder polyps are typically an incidental finding that affects approximately 5% of the population, with a higher percentage in Asian populations. Polyps can be cancer (adenocarcinoma), benign neoplasia (typically adenomas), or cholesterolosis (a clinically insignificant accumulation of cholesterol on the wall of the gallbladder). Polyps that are larger than 20 mm almost always represent a malignancy. Such patients should undergo radical cholecystectomy and lymph node dissection, an operation that is discussed elsewhere in this text. Polyps between 10 and 20 mm in size are at higher risk of malignancy, but when present, such cancers are usually in an early stage. As such, these patients are typically treated with laparoscopic cholecystectomy without liver resection. Polyps less than 10 mm in size have a low risk of cancer and can be observed with surveillance ultrasound to monitor for growth, which can be done on a yearly basis initially. Multiple small polyps usually signify cholesterolosis, and the gallbladder should be removed only if the patient complains of biliary colic symptoms.

Porcelain gallbladder refers to a calcification of the entire gallbladder wall
and has an associated risk of gallbladder cancer. Earlier studies estimated the incidence of gallbladder cancer to be between 12% and 60%, but recent studies suggest that the overall risk is lower, at 7% or less in more recent series.\textsuperscript{28,29} Traditionally, radiographic evidence of porcelain gallbladder was seen as an indication for cholecystectomy, but this algorithm has been challenged by some recent authors who recommend a strategy of surveillance imaging in the absence of another indication for cholecystectomy, such as biliary colic.\textsuperscript{29} Early in the era of minimally invasive surgery, porcelain gallbladder was seen as a contraindication to the use of a laparoscopy,\textsuperscript{30} but this dogma has also largely been abandoned, and it is now viewed as a perfectly safe initial approach to such patients.\textsuperscript{31}

**Choledocholithiasis and Gallstone Pancreatitis**

Although covered in further detail elsewhere in this text, choledocholithiasis and gallstone pancreatitis are important additional indications for laparoscopic cholecystectomy. It is important to understand that in the setting of these diseases, cholecystectomy is a prophylactic operation, rather than a therapeutic one, performed to prevent further migration of gallstones into the CBD. Therefore, when treating patients with choledocholithiasis, the surgeon must come up with a separate plan for dealing with the CBD stone. There are 3 options: either via laparoscopic CBD exploration at the time of cholecystectomy, or with ERCP before or after cholecystectomy. In patients with gallstone pancreatitis, cholecystectomy should be delayed until after the patient’s pancreatic inflammation resolves, although in most cases, the gallbladder should be removed during the same hospitalization in order to prevent early recurrences.

**CONTRAINDICATIONS TO LAPAROSCOPIC CHOLECYSTECTOMY**

The number of absolute and relative contraindications to performing laparoscopic cholecystectomy has decreased over the past 20 years as minimally invasive surgical instrumentation and skills have improved (Table 62-3). Absolute contraindications include the inability to tolerate general anesthesia or laparotomy, refractory coagulopathy, and diffuse peritonitis.
with hemodynamic compromise. Diffuse peritonitis with hemodynamic compromise represents a surgical emergency in which attempted laparoscopic cholecystectomy is not prudent, because the etiology is not clear or secure and the pneumoperitoneum may lead to vascular collapse. Standard open laparotomy allows rapid determination of the etiology and more expeditious management of the disorder. Suspicion of gallbladder malignancy mandates that standard open resection be undertaken. This is because of persistent concerns regarding adequacy of resection and the possibility of gallbladder perforation (occurring in 20%-30% of laparoscopic cholecystectomies) with intraperitoneal dissemination of cancer.

**TABLE 62-3: CONTRAINDICATIONS TO LAPAROSCOPIC CHOLECYSTECTOMY**

**Absolute**
Unable to tolerate general anesthesia  
Refractory coagulopathy  
Gallbladder carcinoma

**Relative**
Cholangitis  
Diffuse peritonitis  
Cirrhosis and/or portal hypertension  
Cholecystoenteric fistula

Relative contraindications are dictated primarily by the surgeon’s philosophy and experience. These include previous upper abdominal surgery with extensive adhesions, cirrhosis, portal hypertension, severe cardiopulmonary disease, morbid obesity, and pregnancy. In most patients, little is lost by initiating a laparoscopic cholecystectomy with conversion to laparotomy if the laparoscopic approach is deemed too risky.

Pregnancy is a controversial relative contraindication to laparoscopic cholecystectomy because of the unknown effects of prolonged carbon dioxide (CO₂) pneumoperitoneum on the fetus. Laparoscopic cholecystectomy can be performed safely during pregnancy but only with great care. The timing of cholecystectomy during pregnancy is a topic of controversy and was
traditionally limited to the second trimester of gestation after organogenesis is complete and prior to the uterine fundus reaching a size and height that encroaches on the operative field. However, there are no data to suggest that laparoscopy during the first trimester is more dangerous, and current society recommendations are generally in favor of performing laparoscopic cholecystectomy at any point during pregnancy as soon as symptoms arise. Open insertion of the initial port in a supraumbilical or right upper quadrant position should be used to avoid injury to the gravid uterus, and the insufflation pressure should be limited to less than 12 mm Hg to avoid respiratory embarrassment and decreased vena caval return. Also, maternal hyperventilation with close monitoring of end-tidal CO$_2$ should be undertaken to prevent fetal acidosis. When visualization of the biliary tree is required, laparoscopic ultrasound is used in place of cholangiography in order to limit fetal radiation exposure. Finally, perioperative consultation with an experienced obstetrician is advisable, as is perioperative fetal heart monitoring.

Early experience suggested that acute cholecystitis was a relative contraindication to performing laparoscopic cholecystectomy. However, as general surgeons have gained more experience with laparoscopic cholecystectomy and laparoscopy in general, it has uniformly become the preferred initial approach to patients with cholecystitis. There is clearly a higher rate of conversion in the setting of acute cholecystitis. In particular, after 72 hours, the rate of conversion increases significantly. One should not hesitate to convert to an open cholecystectomy if significant adhesions or inflammation precludes safe dissection during laparoscopy.

**OPERATIVE TECHNIQUE**

**Anatomy**

The classic anatomy of the biliary tree is present in only 30% of individuals, so it may be said that anomalies are the rule, not the exception. As with any procedure, the knowledge of normal anatomy and common variants is critical to the success of surgical intervention. The cystic duct may join the CBD at an acute angle, travel parallel to the common duct for several centimeters prior to insertion, insert into the right hepatic duct, or be congenitally absent.
The cystic artery usually arises from the right hepatic artery, but one must be absolutely sure that the cystic artery is visualized entering the gallbladder wall. Occasionally the right hepatic artery will loop up onto the surface of the gallbladder, and a very short cystic artery will arise. Furthermore, there can often be a posterior cystic artery, which can easily be injured if not recognized. The CBD begins at the junction of the cystic duct and the common hepatic duct and passes inferiorly to the ampulla of Vater. Its normal diameter is less than 6 mm, although it may be larger in elderly patients and those with biliary obstruction.

It is important to clearly identify the structures within the hepatocystic triangle, which is the ventral aspect of the area bounded by the gallbladder wall and cystic duct, the liver edge, and the common hepatic duct. Contained within the hepatocystic triangle is the eponymic Calot triangle: The boundaries of the Calot triangle include the cystic duct, cystic artery, and common hepatic duct. Aberrant anatomy is a well-recognized risk factor for biliary injury. An aberrant right hepatic duct is the most common anomaly causing problems during laparoscopic cholecystectomies. The most dangerous variant is when the cystic duct joins a low-lying aberrant right sectoral duct. Injuries to these ducts are underreported since occlusion of an aberrant duct may be asymptomatic and even unrecognized (Fig. 62-2).
**FIGURE 62-2**  Biliary anatomy variations. **A.** Normal anatomy. **B.** Cystic duct insertion on right hepatic duct. **C.** Anterior or posterior spiral insertion of cystic duct. **D, E, and F.** Common variants of accessory right hepatic duct (RHD).

**Patient Preparation**

As with any abdominal operation, patients are fasted for a minimum of 8 hours prior to the operation. Patients without major comorbidities are generally scheduled as outpatient procedures. Prophylactic antibiotics are up to the surgeon’s discretion; evidence suggests that most patients have a very low risk of perioperative infection, and perioperative antibiotics have not been shown to significantly decrease this risk. Antiembolic stockings and sequential compression devices are placed on both legs to avoid pooling of
blood in the lower extremities by the reverse Trendelenburg position generally used during this operation. Patients at higher risk for lower extremity deep vein thrombosis (DVT) are additionally given prophylactic-dose subcutaneous unfractionated or low-molecular-weight heparin. Following induction of general endotracheal anesthesia, an orogastric tube should be placed to decompress the stomach. The abdomen is shaved and prepared in standard sterile fashion with particular care taken to rid the umbilicus of all debris.

**Laparoscopic Cholecystectomy**

**OPERATING ROOM SETUP**

Most surgeons use 2 video monitors, 1 on each side of the operating table above the patient’s shoulders to facilitate visualization by both the surgeon and assistant. Using the American technique, the surgeon stands to the left of the patient and the first assistant stands to the patient’s right (Fig. 62-3). If a laparoscopic video camera operator is used, he or she stands to the left of the surgeon. In the French technique, the patient’s legs are abducted and the surgeon stands between the legs.
PNEUMOPERITONEUM

A working space, provided by a pneumoperitoneum, is essential for the surgeon to see and to operate within the abdominal cavity. CO$_2$ has the advantage of being noncombustible and rapidly absorbed from the peritoneal cavity. It may, however, lead to hypercarbia in patients with significant cardiopulmonary disease. The most common location for initial peritoneal entry is at the midline near the umbilicus. Supraumbilical or infraumbilical incisions may be made in vertical, horizontal, or curvilinear orientations based on surgeon’s preference. Pneumoperitoneum can be established by either a closed or an open technique. In the closed technique, CO$_2$ is insufflated into the peritoneal cavity through a Veress needle, which is subsequently replaced with a laparoscopic port placed blindly into the abdominal cavity. In the open technique, a laparoscopic port is inserted under direct vision into the peritoneal cavity via a small incision; only after ensuring definitive and safe peritoneal entry is the pneumoperitoneum established. There are advantages and disadvantages to both techniques. Surgeons performing laparoscopic cholecystectomy should learn both and use them selectively based on the patient’s body habitus and previous surgical history.

PORT PLACEMENT AND EXPOSURE

Depending on the surgeon’s preference, a 5- or 10-mm laparoscope is inserted into the abdomen through the periumbilical port and the abdominal cavity is visually explored. It is generally advantageous to use an angled (30- or 45-degree) laparoscope rather than a 0-degree scope, because the angled scopes enable obtaining multiple views of the same operative field. The patient is then placed in a reverse Trendelenburg position of 30 degrees while rotating the table to the left by 15 degrees. This maneuver allows the colon and duodenum to fall away from the liver edge. The falciform ligament and both lobes of the liver are examined closely for abnormalities. The gallbladder can usually be seen protruding beyond the edge of the liver, and the degree of inflammation surrounding the gallbladder can be gauged.

Two small accessory subcostal ports are then placed under direct vision.
The first 5-mm trocar is placed along the right anterior axillary line between the 12th rib and the iliac crest. This trocar should be at least 2 finger breadths inferior to the costal margin and as lateral as possible while remaining anterior to the ascending colon. A second 5-mm port is inserted in the right subcostal area in the midclavicular line. Grasping forceps are placed through these 2 ports to secure the gallbladder. The assistant manipulates the lateral grasping forceps, which are used to grasp the fundus and elevate the liver. The fourth working port is then inserted through an incision in the midline of the epigastrium (Fig. 62-4). This trocar is usually inserted approximately 5 cm below the xiphoid process, but the precise position and angle depend on the location of the gallbladder as well as the size of the medial segment of the left lobe of the liver. It should be placed so that the trocar enters the peritoneum to the right of the falciform ligament.

![Port placement.](image-url)

Dissecting forceps are then inserted and directed toward the gallbladder neck. One should note that the orientation of the laparoscope is generally parallel to that of the cystic duct when the fundus is elevated, whereas the instruments placed through the other 3 ports enter the abdomen at right angles to this plane. The surgeon uses a dissecting forceps to raise a serosal
fold of the most dependent portion of the fundus. The assistant’s heavy grasping forceps are then locked onto this fold using either a spring or ratchet device. With these axillary grasping forceps, the fundus of the gallbladder is then pushed in a lateral and cephalad direction, rolling the entire right lobe of the liver cranially.

This maneuver is complicated in patients with a fixed, cirrhotic liver or a heavy, friable liver because of fatty infiltration. In patients with few adhesions to the gallbladder, pushing the fundus cephalad exposes the entire gallbladder, cystic duct, and porta hepatis. Most patients, however, have adhesions between the gallbladder and the omentum, hepatic flexure, and/or duodenum. These adhesions are generally avascular and may be lysed bluntly by grasping them with dissecting forceps at their site of attachment to the gallbladder wall and gently stripping them down toward the infundibulum. Extreme caution should be taken to avoid damage to surrounding structures. Use of electrocautery may accidentally damage the unvisualized CBD or proximally located duodenum. After exposing the infundibulum, blunt grasping forceps held in the surgeon’s left hand and placed through the midclavicular trocar are used to grasp and place traction on the neck of the gallbladder.

DISSECTION

The infundibulum is grasped, placing traction on the gallbladder in a lateral direction to distract the cystic duct from the CBD (Fig. 62-5). Fine-tipped dissecting forceps (Maryland) are used to dissect away the overlying fibroareolar structures from the infundibulum of the gallbladder. The dissection should begin from a known structure, for example, the gallbladder, rather than in an unknown area, to avoid damage to the underlying structures such as a bile duct or hepatic artery. The dissection initially commences 4 or 5 cm proximal to the neck of the gallbladder and proceeds distally, such that a modified “top-down” technique is employed. The objective of the initial dissection is to free the gallbladder from its bed such that there is a window beneath it through which the liver substance can be seen. This dissection is typically initiated on the lateral (ie, anatomic right) side of the gallbladder to avoid approaching the cystic duct and artery until the anatomy, including the true edge of the gallbladder, has been more clearly defined. During this portion of the dissection, the infundibulum should be retracted medially and
superiorly. Blunt dissection is used to create a “window” in the lateral edge of the peritoneum overlying the gallbladder. Once this window has been opened, it is safe to use an L-shaped electrocautery hook to open the rest of the lateral peritoneal edge, heading toward the gallbladder fundus, away from the cystic duct and portal structures. When applying electrocautery, it is important to pull the instrument away from the gallbladder to avoid a perforation or other injury to underlying structures. We then retract the infundibulum laterally and inferiorly and repeat this process to open the medial peritoneal edge of the gallbladder.

![Retraction of the gallbladder](image)

**FIGURE 62-5** Retraction of the gallbladder.

After both peritoneal edges have been opened high up onto the gallbladder fundus, the hepatocystic triangle is maximally opened and converted into a trapezoid shape by retracting the infundibulum of the gallbladder inferiorly and laterally while maintaining the fundus under traction in a superior and medial direction. A lymph node usually lies on the surface of the cystic artery, and occasionally it is necessary to use a brief application of low-wattage electrosurgical coagulation to obtain hemostasis as the lymph node is bluntly swept away. To expose the reverse of the Calot triangle, the
The infundibulum of the gallbladder is pulled in a superior and medial direction. The use of an angled laparoscope facilitates viewing both sides of the hepatocystic triangle when used in combination with these retraction techniques. After clearing the structures from the apex of the triangle, the junction between the infundibulum and the origin of the proximal cystic duct can be tentatively identified. The strands of peritoneal, lymphatic, and neurovascular tissue are stripped away from the cystic duct to clear a segment from the surrounding tissue. Curved dissecting forceps are helpful in creating a window around the posterior aspect of the cystic duct to skeletonize the duct itself. Alternatively, the tip of the hook cautery can be used to encircle and expose the duct. It is generally unnecessary and potentially harmful to dissect the cystic duct down to its junction with the CBD. The cystic artery is separated from the surrounding tissue by similar blunt dissection at this time. If the cystic artery crosses anterior to the duct, the artery may require dissection and division prior to approaching the cystic duct, although if at all possible, this should be avoided until all relevant anatomy has been clearly identified.

The neck of the gallbladder is thus dissected away from its liver bed, leaving a large window at its base through which the liver parenchyma is visualized. At least one-third of the cystic plate (ie, gallbladder bed) should be exposed in this manner. At this point, there should be 2, and only 2, structures (the cystic duct and artery) crossing this window—this is the “critical view of safety,” which should be demonstrated prior to clipping or cutting any tubular structures. To reiterate, no structure should be divided until the cystic duct and cystic artery are unequivocally identified. Developing this critical view of safety is an essential step to minimize the chance of bile duct injury during laparoscopic cholecystectomy (Fig. 62-6).
INTRAOPERATIVE EVALUATION FOR CHOLEDOCHOLITHIASIS

After initially dissecting the proximal cystic duct, the CBD should be imaged if there is any concern for choledocholithiasis or questions regarding the biliary anatomy. Indications for intraoperative imaging of the CBD include any indication of choledocholithiasis based on the patient’s history, physical examination, laboratory tests, preoperative imaging, or intraoperative findings. Imaging can be achieved by intraoperative cholangiography (IOC) or intracorporeal laparoscopic ultrasonography (LUS). Prior to either procedure, a clip is applied high on the cystic duct at its junction with the gallbladder to prevent stones migrating down the duct during subsequent manipulation. To perform IOC, the anterolateral wall of the cystic duct is incised and dissecting forceps are used to gently compress the cystic duct systematically back toward the gallbladder, thereby milking stones away from the CBD and out of the ductotomy. A 4- or 5-Fr catheter is inserted into the duct through a hollow, 5-mm metal tube that has an appropriate gasket to
prevent carbon dioxide leakage around the catheter itself. The cholangiography catheter is inserted into the cystic duct, and a clip is applied loosely to secure the catheter in place. If the introducer has grasping jaws (ie, an Olsen clamp), it can be used to secure the catheter into the duct. Alternatively, catheters equipped with balloons proximal to the tip may be used for fixation. Cholangiography is performed by real-time fluoroscopy after injecting 10 to 20 mL of water-soluble contrast medium. We typically mix the contrast at half-strength (50%/50% contrast-saline mix) to avoid obscuring small stones in the CBD and use digital subtraction fluoroscopy to help eliminate other radiopaque elements, such as the vertebrae, and thus define the biliary anatomy more clearly. The fluoroscopy images should be inspected for the following: (1) the length of cystic duct and location of its junction with the CBD; (2) the diameter of the CBD; (3) the presence of luminal filling defects within the CBD; (4) free flow of contrast into the duodenum; and (5) anatomy of the extrahepatic and intrahepatic biliary tree (Fig. 62-7). After the cholangiocatheter is removed, the cystic duct is doubly clipped below the ductotomy with care to avoid the wall of the CBD and then divided. The posterior jaw of the clip applier must be visualized beyond the duct or artery prior to applying each clip in order to avoid injuring the surrounding structures. Great care should be taken so that the CBD is not tented up into the clip. If the cystic duct is particularly large or friable, it may be preferable to replace one of the clips with a suture, either hand-tied or a preformed loop with slip knot.
Evaluation of the CBD by LUS is an alternative to cholangiography. Several studies performed at open cholecystectomy reported intracorporeal ultrasonography to be more accurate than operative cholangiography in assessing the CBD for stones (97%-99% vs 89%-94%). With LUS, the transducer has a higher frequency with improved resolution compared to those used with transabdominal ultrasonography. In experienced hands, LUS appears to be as accurate as cholangiography for demonstrating choledocholithiasis but can be performed more rapidly. In a recent prospective multicenter trial with 209 laparoscopic cholecystectomy patients, the time to perform LUS (7 ± 3 minutes) was significantly less than that of IOC (13 ± 6 minutes). The study showed that LUS was more sensitive for detecting stones but that IOC was better in delineating intrahepatic anatomy and defining anatomic anomalies of the ductal system. The authors concluded that the 2 methods of duct imaging were complementary. Despite these promising data, more clinical experience will be necessary to establish the appropriate role of LUS for the detection of choledocholithiasis during laparoscopic cholecystectomy.
COMPLETION OF CHOLECYSTECTOMY

The cystic duct is clipped using an endoscopic clip applier and divided using scissors. Two clips are placed distally on the cystic duct, and 1 clip is placed toward the gallbladder (Fig. 62-8). For cystic ducts that are large or friable, a preformed endoloop is preferable for ligating the distal cystic duct. After the duct is divided, the cystic artery is dissected from the surrounding tissue for an adequate distance to permit placement of 3 clips. The surgeon must determine that the structure is indeed the cystic artery and not the right hepatic artery looping up onto the neck of the gallbladder or an accessory or replaced right hepatic artery. After an appropriate length of cystic artery has been dissected free, it is clipped proximally and distally prior to transection (Fig. 62-9). Electrocautery should not be used for this division, as the current may be transmitted to the proximal clips, leading to subsequent necrosis and hemorrhage.

FIGURE 62-8 Clipping the cystic duct.
The ligated stumps of the cystic duct and the artery are then examined to ensure that there is no leakage of either bile or blood and that the clips are placed securely and compress the entire lumen of the structures without scissoring or impinging on adjacent tissues. A suction-irrigation catheter is used to remove any debris or blood that has accumulated during the dissection. Separation of the gallbladder away from its hepatic bed is then initiated using an electrosurgical probe to coagulate small blood vessels and lymphatics. While maintaining cephalad traction on the fundus of the gallbladder with the axillary forceps, the midclavicular forceps pulls the neck of the gallbladder anterosuperiorly and then alternatively medially and laterally to expose and place the tissue connecting the gallbladder to its fossa under tension. An electrocautery spatula or hook is used to coagulate and divide the tissue. Intermittent blunt dissection will facilitate exposure of the proper plane (Fig. 62-10).
Dissection of the gallbladder fossa continues from the infundibulum to the fundus, progressively moving the midclavicular grasping forceps cephalad to allow maximal countertraction. The dissection proceeds until the gallbladder is attached by only a thin bridge of tissue. At this point, prior to completely detaching the gallbladder, the hepatic fossa and porta hepatis are once again inspected for hemostasis and bile leakage. Small bleeding points are coagulated, and the right upper quadrant is liberally irrigated and then aspirated dry while checking for any residual bleeding or bile leakage. The final attachments of the gallbladder are divided, and the liver edge is again examined for hemostasis.

After the cholecystectomy has been performed, the gallbladder must be removed from the abdominal cavity. The gallbladder may be placed within an entrapment sac prior to extracting it through the abdominal wall (Fig. 62-11). This is recommended particularly if the gallbladder has been perforated intraoperatively or if the specimen is large. If the stone burden is small, the gallbladder can be extracted at the subxiphoid port site. Usually, the gallbladder is most easily removed at the umbilical port site where there are no muscle layers anterior to the fascial plane. Also, if the fascial opening needs to be enlarged because of large or numerous stones, extension of the
umbilical incision causes less postoperative pain and has better cosmesis than does enlarging the subxiphoid incision. The laparoscope is removed from the umbilical port and placed through the epigastric port. Large “claw” grasping forceps are introduced through the umbilical port to grasp the infundibulum of the gallbladder. The forceps, trocar, and gallbladder neck are then retracted as a unit through the umbilical incision. The neck of the gallbladder is thus exteriorized through the anterior abdominal wall with the fundus remaining within the abdominal cavity. If the gallbladder is not distended with bile or stones, it can be simply withdrawn with gentle traction. In many cases, a suction catheter introduced through an incision in the gallbladder neck is used to aspirate bile and small stones. Stone forceps can also be placed into the gallbladder to extract or crush calculi if necessary. Occasionally, the fascial incision must be extended to extract larger stones or thick-walled gallbladders.

FIGURE 62-11 Placing gallbladder in entrapment bag.

Each incision is infiltrated with bupivacaine for postoperative analgesia. The fascia of the umbilical incision is closed with 1 or 2 large absorbable sutures in an interrupted or figure-of-8 fashion. Closure of the subxiphoid
fascia is optional, as visceral herniation is unlikely to occur because of the oblique entry angle of the trocar into the abdominal cavity and its location anterior to the falciform ligament. The skin of the subxiphoid and umbilical incisions is closed with subcuticular absorbable sutures. The skin incisions at both 5-mm port sites can be closed with absorbable sutures, adhesive strips, or skin closure adhesives. The orogastric tube is removed in the operating room, and the patient is transferred to the postanesthesia care unit. Patients are allowed out of bed as soon as they are fit enough to walk, and more than 90% of patients are discharged from the hospital within 24 hours. Fit patients who have been preoperatively selected may be safely discharged within 6 hours following surgery. Patients are evaluated 1 week following surgery. At this time, more than 95% of patients are back to a normal routine, and most return to work immediately following their clinic visit.

ADVANTAGES AND DISADVANTAGES

The advantages of laparoscopic cholecystectomy over other therapies for gallstone disease are multiple (Table 62-4). Unlike nonresective techniques for gallstone ablation, laparoscopic cholecystectomy removes the diseased gallbladder along with its stones. Relative to traditional open cholecystectomy, postoperative pain and intestinal ileus are diminished with laparoscopic cholecystectomy. The small size of the fascial incisions allows rapid return to heavy physical activities. The small incisions are also cosmetically more appealing than is the large incision used during traditional cholecystectomy. The patient can usually be discharged from the hospital either on the same day or the day following operation and can return to full activity within a few days. These factors lead to overall decreased cost of laparoscopic cholecystectomy compared to its traditional open counterpart.

TABLE 62-4: ADVANTAGES AND DISADVANTAGES OF LAPAROSCOPIC CHOLECYSTECTOMY COMPARED WITH OPEN CHOLECYSTECTOMY
There are, however, several potential disadvantages of laparoscopic cholecystectomy. As opposed to nonresective treatments for gallstones, patients must be acceptable candidates for general anesthesia and possible laparotomy. Three-dimensional depth perception is limited by the 2-dimensional monocular image of the videoscope. It is more difficult to control significant hemorrhage using laparoscopic technology than in an open surgical field. There is also less haptic discrimination of structures using laparoscopic instruments as opposed to direct digital palpation during open cholecystectomy. CO$_2$ insufflation to create the pneumoperitoneum is associated with a number of potential risks, including reduction of vena caval flow and systemic hypercarbia with acidosis.

### SPECIAL CONSIDERATIONS

**Conversion to Open Operation**

Surgeons performing laparoscopic cholecystectomy should not think of conversion to open operation as a complication, but rather a sound clinical judgment, and hence not hesitate to convert to a traditional open cholecystectomy if the anatomy is unclear, if complications arise, or if there is failure to make reasonable progress in a timely manner. Some complications requiring laparotomy are obvious, such as massive hemorrhage or major injury to the bile duct. Open laparotomy allows the additional tool of manual palpation and haptic sensation and should be performed when the

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Less pain</td>
<td>Lack of depth perception</td>
</tr>
<tr>
<td>Shorter hospitalization</td>
<td>Difficult in setting of dense adhesions/inflammation</td>
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<tr>
<td>Early return to full activity</td>
<td>More difficult to control hemorrhage</td>
</tr>
<tr>
<td>Decreased wound complications</td>
<td>Potential CO$_2$ insufflation complications</td>
</tr>
<tr>
<td>(infection and hernia)</td>
<td></td>
</tr>
<tr>
<td>Decreased total costs</td>
<td>Slight increase in bile duct injuries</td>
</tr>
</tbody>
</table>
anatomy cannot be delineated because of inflammation, adhesions, or anomalies. Fistulae between the biliary system and bowel are rare, but may require laparotomy for optimal management. The demonstration of potentially resectable gallbladder carcinoma also dictates an open exploration. Finally, CBD stones that cannot be removed laparoscopically and are unlikely to be extracted endoscopically because of Billroth II anastomosis, previously failed ERCP, should be converted to open operation without hesitation.

Open Cholecystectomy

The technical aspects of performing an open cholecystectomy have not changed significantly since Langenbuch’s description of this procedure more than 100 years ago. Although this operation can be performed safely through a midline, paramedian, or right subcostal incision, most surgeons prefer the right subcostal (Kocher) incision. Adequate exposure of the gallbladder and the hepatoduodenal ligament is the key to performing a safe cholecystectomy. Laparotomy sponges may be packed temporarily between the dome of the liver and the diaphragm, and appropriate self-retaining retractors should be inserted to optimize visualization of the hepatoduodenal ligament and its structures. The hepatic flexure of the colon is packed or retracted inferiorly, and the medial segment of the left liver lobe is retracted superiorly. When a large distended gallbladder is encountered, removal can be facilitated by decompressing the gallbladder. Adhesions of omentum or viscera adjacent to the gallbladder are divided with sharp dissection or electrocautery.

Meticulous dissection and positive identification of the cystic duct, its entry into the CBD, and the cystic artery are mandatory and significantly reduce the likelihood of bile duct injury. Most experienced surgeons prefer to identify these important structures before beginning dissection of the gallbladder from the hepatic bed. The fundus and infundibulum of the gallbladder are grasped with curved clamps. The fundus is retracted anteriorly and superiorly and the infundibulum inferiorly and laterally, exposing the structures of the Calot triangle. Caudal counter-retraction of the hepatoduodenal ligament stretches and exposes the porta hepatis, placing the peritoneum overlying the cystic duct and artery on tension. This maneuver may be accomplished with a retractor, although the left hand of the first assistant effectively retracts the duodenum. The surgeon introduces the left
index finger into the foramen of Winslow and palpates for calculi in the CBD. Acute inflammation or chronic scarring may preclude approaching the infundibulum first; many surgeons prefer to dissect the fundus initially (ie, a fundus first or top-down technique), and the ductal and vascular structures subsequently, only after the organ has been separated from the liver. Careful ligation of the cystic duct is essential not only in preventing a biliary leak, but also in reducing the possibility of bile duct injury and stricture. Ligation of the cystic duct in close proximity to its junction with the CBD has long been considered an essential component of open cholecystectomy. Experience with laparoscopic cholecystectomy suggests that the length of the cystic duct stump is not a critical factor and probably does not significantly contribute to postcholecystectomy syndrome, a poorly defined clinical entity characterized by pain after gallbladder removal. Therefore, it is safer to divide the cystic duct closer to the gallbladder infundibulum once a “critical view of safety” has been obtained and to avoid dissection in proximity to the CBD altogether. The cystic artery should be dissected, secured, and divided near the surface of the gallbladder. This will reduce bleeding associated with division of the peritoneum investing the gallbladder and separation of areolar tissue between the gallbladder and the liver. Intraoperative cholangiography can be performed at the discretion of the surgeon.

Throughout the procedure, care should be exercised to minimize spillage of bile into the peritoneal cavity. Drains are not mandatory and are indicated only if the surgeon is concerned about identifying or controlling a possible bile leak. Common pitfalls are usually related to inadequate exposure, severe inflammation, bleeding, and anatomic variants, which can lead to injury of portal structures, including the CBD and the hepatic artery or its branches. With a short cystic artery, the right hepatic artery must be carefully identified. Similarly with a short cystic duct, careful dissection and high ligation of the cystic duct near the gallbladder should be employed to avoid injury to the CBD. In fact, in the face of severe inflammation with obliteration of normal tissue planes, it may be safest to perform a subtotal cholecystectomy, leaving a portion of the infundibulum in situ (after removing all stones) and suture ligating the mucosal side of the cystic duct origin. If there is unintentional gallbladder puncture, a second clamp or purse string suture can be applied to prevent gallbladder bile and stone spillage. Before closing the abdominal incision, bleeding and bilious drainage must be controlled. Structures in the porta hepatis are reexamined, with special attention to the cystic duct stump.
The subhepatic space is irrigated with warm saline and all irrigants are evacuated. The incision is usually closed in 1 or 2 layers. The skin can be closed with sutures or staples.

**Acute Cholecystitis**

Acute cholecystitis may be treated successfully by laparoscopic cholecystectomy. Intervention during the early phase often reveals an inflamed, edematous, thick-walled, and tensely distended organ. To gain adequate traction on the gallbladder with the grasping forceps, it may be necessary to decompress the gallbladder by aspirating its contents with a large-gauge needle or suction irrigator. As long as the inflammation is limited to the gallbladder, laparoscopic cholecystectomy is usually technically feasible. However, if inflammation extends to the porta hepatis, great care must be taken in proceeding with the operation. The normally thin, minimally adherent tissue that invests the cystic duct and artery is markedly thickened and edematous and may not readily separate from these structures with the usual blunt dissection techniques. The duct wall also may be edematous, thus making its external diameter similar to the gallbladder neck and CBD. If the anatomy is unclear, cholangiography must be performed before clipping or dividing tissue. When acute inflammation has been present for several days or weeks before operation, the pericholecystic tissue planes may be obliterated by thick, woody tissue that is difficult to dissect bluntly. The surgeon may therefore need to convert to open cholecystectomy if the minimal access approach is initially attempted during this subacute phase. There is no harm in inserting the laparoscope and assessing the right upper quadrant. The decision to convert to an open operation is a matter of judgment, based on the existing anatomy, local conditions, and the surgeon’s experience and confidence in his or her ability to complete the procedure using minimal access techniques.

Several authors have reported performing laparoscopic cholecystectomy in the face of acute inflammation with success but with a higher conversion rate than for elective laparoscopic cholecystectomy.\textsuperscript{41-43} In a prospective study of 105 patients randomized to early laparoscopic cholecystectomy (within 24 hours of diagnosis of acute cholecystitis) versus delayed laparoscopic cholecystectomy (6-8 weeks later), there was no significant difference in conversion rate (early 21% vs delayed 24%), postoperative analgesic
requirement, or number of postoperative complications. The early group did have a longer operative time (123 vs 107 minutes; \( p = .04 \)), but total hospitalization was shorter (8 vs 12 days; \( p = .001 \)). Rattner and associates retrospectively reviewed 20 patients who underwent attempted laparoscopic cholecystectomy for acute cholecystitis and examined factors that were predictive of a successful procedure. Seven of the 20 patients (35%) required conversion to open cholecystectomy. The interval from admission to cholecystectomy in the successful cases was 0.6 days versus 5 days in the cases requiring conversion to open cholecystectomy. Converted cases also had a significantly higher white blood cell (WBC) counts, alkaline phosphatase levels, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores compared to those undergoing successful laparoscopic cholecystectomy. Ultrasonographic findings such as gallbladder distention, wall thickness, and pericholecystic fluid did not correlate with the success of laparoscopic cholecystectomy.

More recent studies have confirmed that laparoscopic cholecystectomy is an equivalent or better option than open surgery for treating acute cholecystitis. In a study of 2 prospectively randomized groups, Johansson and associates reported that there were no differences in postoperative complications or pain when comparing laparoscopic to open cholecystectomy. Using a cohort of almost 1 million patients from the National Hospital Discharge Surveys from 2000 to 2005, Csikesz and associates reported that patients undergoing laparoscopic cholecystectomy for acute cholecystitis have low conversion rates (9.5%) and also lower morbidity (16% vs 36%) and unadjusted mortality (0.4% vs 3%) compared to patients who undergo open cholecystectomy.

It can be concluded that laparoscopic cholecystectomy should be performed immediately after the diagnosis of acute cholecystitis. Delaying surgery allows inflammation to become more intense and neovascularized, thus increasing the technical difficulty of laparoscopic cholecystectomy.

**Intraoperative Gallbladder Perforation**

Perforation of the gallbladder with bile or stone leakage can be a nuisance but should not ordinarily require conversion to open cholecystectomy. Perforation may occur secondary to traction applied by the grasping forceps.
or because of electrosurgical thermal injury during removal of the gallbladder from its bed. In our experience, almost one-third of patients have had intraoperative spillage of bile or stones. Patients with bile spillage have not experienced an increased incidence of infection, prolongation of hospitalization, or postoperative disability, or more adverse long-term complications (mean follow-up of 41 months in 250 consecutive laparoscopic cholecystectomy patients). The only difference between patients with and without bile leakage was that the operating time of patients with a gallbladder perforation was approximately 10 minutes longer, presumably because of the time spent in cleaning up the operative field. When perforation does occur, the bile should be aspirated completely and irrigation used liberally. The hole in the gallbladder is best secured with a grasping instrument and can be sutured or tied with an endoloop. The stones should be retrieved and removed. Gallbladder spillage, when treated in this manner, results in no adverse short- or long-term complications. Escaped stones composed primarily of cholesterol pose little threat of infection. However, pigment stones frequently harbor viable bacteria and may potentially lead to subsequent infectious complications if allowed to remain in the peritoneal cavity. The long-term complications of retained stones, either intra-abdominally with resultant abscess formation or intramurally with resultant port site abscess, have not been prospectively studied, but recent case reports and case series in the surgical literature document a clear potential for long-term infectious complications. The relative infrequency of these complications probably does not justify conversion to open operation in the face of spilled stones, but vigilance in avoidance of perforation, a careful search for escaped stones, the aggressive use of irrigation, and liberal use of a plastic retrieval bag for large and friable gallbladders are recommended.

COMPICATIONS

Laparoscopic Cholecystectomy

Most complications related to laparoscopic removal of the gallbladder are similar to those occurring during traditional open cholecystectomy. These complications include hemorrhage, bile duct injuries, bile leaks, retained stones, pancreatitis, wound infections, and incisional hernias. Other potential
complications are pneumoperitoneum related (gas embolism, vagal reaction, ventricular arrhythmias, or hypercarbia with acidosis) and trocar related (injuries to the abdominal wall, intra-abdominal organs, or major blood vessels). The protective shield on disposable trocars is not an insurance against perforation of intestine or major vessels, especially after previous abdominal operations. Regardless of the make of trocar, during its insertion, one should never aim toward the spine or the location of the great vessels, and a hand is used as a brake to prevent inadvertently introducing the trocar too far. Insertion of the initial trocar, especially when performed in a closed fashion, can cause iatrogenic injury to the bowel, bladder, aorta, iliac artery, or vena cava.\textsuperscript{52,53} When a trocar injury to a major blood vessel is suspected, the patient must be opened immediately without removing the trocar until the involved blood vessel is isolated. In contrast, if the small-bore Veress needle enters a viscus or blood vessel, the operation can generally be completed and the patient monitored closely for signs of complications in the postoperative period.

The laparoscopic trocars may also lacerate blood vessels in the abdominal wall. Prior to removal, each trocar should be visualized from the peritoneal aspect using the laparoscope. If significant hemorrhage is seen, it can generally be controlled with cautery, intraoperative tamponade with a Foley catheter, or a through-and-through suture on each side of the trocar insertion site.

Most serious complications occur early in the surgeon’s experience. For instance, in a multivariate regression analysis of 8839 laparoscopic cholecystectomies in which there were 15 bile duct injuries, the only significant factor associated with an adverse outcome was the surgeon’s experience with the procedure.\textsuperscript{54} The regression model predicted that a surgeon had a 1.7% chance of a bile duct injury occurring in the first case and a 0.17% chance of a bile duct injury in the 50th case.

Of all the potential complications, biliary injuries have received the most attention and are discussed at length elsewhere in this text. Most series quote a major bile duct injury rate of around 0.2% during open cholecystectomy, whereas the incidence of bile duct injuries during laparoscopic cholecystectomy is 0.40% or higher.\textsuperscript{34} These injuries can cause major morbidity, prolonged hospitalization, high cost, and litigation.\textsuperscript{54,55} In addition to the surgeon’s experience and aberrant biliary anatomy, a number of reports
mention chronic inflammation with dense scarring, operative bleeding obscuring the field, or fat in the portal area contributing to the biliary injuries. The classic biliary injury, however, occurs when the CBD or a right hepatic duct is mistaken for the cystic duct and is divided between clips. Many surgeons attribute this misidentification to the direction of traction of the gallbladder, which is pulling the CBD and the cystic duct into alignment, thus making them appear to be one. Other contributing factors to misidentification are a short cystic duct, a large stone in Hartmann’s pouch (making retraction and display of the cystic duct difficult), and tethering of the infundibulum to the CBD by acute or chronic inflammation. Constant awareness of these potential misidentifications and technical causes of biliary injuries is the best method of prevention. If a partial bile duct injury occurs and is recognized intraoperatively, an immediate primary repair, possibly in conjunction with a T-tube, should be performed. A complete transection of the bile duct is a rare injury, and an end-to-end repair is a technically challenging procedure that may require assistance from an experienced hepatobiliary surgeon. When a bile duct injury is discovered in the postoperative period, a coordinated effort by radiologists, endoscopists, and surgeons is necessary to optimize management. There should be no hesitation in asking for the help of a surgeon experienced in biliary repair.

NEW AND INVESTIGATIONAL TECHNIQUES TO PERFORM CHOLECYSTECTOMY

The advent of laparoscopic cholecystectomy provided a dramatic benefit to patients who previously underwent laparotomy for gallbladder disease. While laparoscopy has already set a high bar for cholecystectomy with regard to perioperative and intraoperative outcomes, there are areas of surgical research examining ways that could potentially make the procedure even less invasive.

Single-Incision Laparoscopic Surgery

Single-incision laparoscopic surgery (SILS) is a recent development that involves introducing all operative instruments and devices through a single skin incision, usually at the umbilicus. The proposed benefit of single-incision laparoscopic cholecystectomy over traditional laparoscopic
cholecystectomy is by reducing the overall number of abdominal incisions from 3 or 4 to 1, thus resulting in less perioperative pain and fewer incisional complications. From a technical standpoint, single-port surgery leads to all of the instruments entering the operative field in line with the optics. Triangulation and traction or countertraction are made more difficult, but new instruments are being developed to overcome these limitations.

Although data comparing single-incision to traditional 4-port cholecystectomy are limited, they are beginning to show significant drawbacks to the SILS approach, without the theoretical advantages of decreased pain and convalescence. A randomized trial by Jorgensen and colleagues compared the 2 techniques and found the single-incision approach to result in prolonged operative times without any difference in postoperative pain scores.\textsuperscript{57} However, there was an advantage to the single-incision approach in terms of cosmesis ratings at 12 months after surgery. The most comprehensive trial comparing the 2 techniques thus far is a multicenter trial by Marks and colleagues that randomized 200 patients. It showed that perioperative outcomes and complication rates were similar but that single-incision cholecystectomy actually resulted in more postoperative pain and a higher incidence of incisional hernia formation at 1 year after surgery than a traditional 4-trocar approach (8.4% vs 1.2%).\textsuperscript{58,59} Based on these data, most surgeons have abandoned single-incision laparoscopic cholecystectomy except in the rare instance that the cosmetic outcome of the incisions is of great importance to a particular patient.

**Natural Orifice Transluminal Endoscopic Surgery**

Natural orifice transluminal endoscopic surgery (NOTES) is an investigational approach to intra-abdominal surgery that aims to reduce and eventually eliminate all abdominal incisions by accessing the peritoneum through natural orifice routes including transoral or transgastric, transvaginal, and transanal or transcolonic. By eliminating abdominal incisions, the hypothesis is that there will be less pain, fewer complications, and decreased morbidity associated with abdominal incisions. These benefits are proposed to include decreased incisional hernias, wound infections, and postoperative pain and improved cosmesis. Given the current state of technology and lack of appropriate instrumentation, few pure NOTES cholecystectomies have
been performed worldwide.\textsuperscript{60,61} NOTES hybrid procedures, where a laparoscopic instrument is used in conjunction with the natural orifice devices, have been performed in greater numbers, although only in a relatively few specialized centers. These were initially performed via a transgastric approach using a flexible gastroscope inserted transorally. This approach proved to be incredibly technically challenging and time-consuming, while adding potential complications due to closure of the resulting gastrotomy and esophageal injury during transoral gallbladder extraction. For these reasons, this approach has since been abandoned.

Transvaginal hybrid NOTES cholecystectomy, using a standard rigid laparoscopic inserted through a culpotomy in the posterior fornix in conjunction with 1 or 2 additional transabdominal ports for dissection has proved to be a safe and viable procedure that is currently being performed in select centers, mostly in Germany and South America. So far, the limited outcomes data resulting from this technique have been encouraging. Several trials (both retrospective and randomized comparisons) have compared transvaginal hybrid NOTES cholecystectomy with a traditional laparoscopic approach and found NOTES to result in decreased postoperative pain with similar rates of perioperative complications.\textsuperscript{62,63} While these initial results are promising, NOTES cholecystectomy remains an investigational procedure that should only be performed in the context of an Institutional Review Board–approved research protocol.

CONCLUSION

Cholecystectomy remains one of the most common operations performed in the United States and worldwide. Laparoscopic cholecystectomy is currently the standard for treatment of gallstone and gallbladder disease. There are numerous advantages of laparoscopic cholecystectomy over open cholecystectomy, including decreased pain, length of stay, recovery time, and incisional complications, and improved cosmesis. However, occasionally anatomic or physiologic considerations will hinder or preclude the minimal access approach, and conversion to an open operation in such cases reflects sound clinical judgment and should not be considered a complication. The goal of any cholecystectomy, whether laparoscopic or open, is the safe removal of the gallbladder while avoiding injury to the CBD at all costs.
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With advanced endoscopic and laparoscopic techniques readily accessible to the treating surgeon, determining the wisest path to the successful treatment of choledocholithiasis and cholangitis has become more challenging. Nevertheless, a large number of options allow one to tailor specific therapy to each individual clinical situation in order to achieve the highest probability of safety and success. In this chapter, we offer the reader a review of the methods available for the diagnosis and treatment of common bile duct (CBD) stones and cholangitis so that treatment plans can be developed that are patient-specific and have the highest chance of success.

CHOLEDОCHОLITHIАSIS

Classification and Epidemiology

A common entity in Western societies, gallstones are found in approximately 15% of Americans and result in 700,000 cholecystectomies a year. The annual cost of medical care for gallstones is almost $6.5 billion compared
with colorectal cancer ($9.5 billion), viral hepatitis ($3.4 billion), and gas-
troesophageal reflux disease (GERD) ($12.6 billion).\textsuperscript{1,2} CBD (downstream of the confluence of the hepatic ducts) stones have been noted in 10% to 15% of patients with cholelithiasis, and this incidence increases with age to over 80% in those who are over 90 years old.\textsuperscript{3} Choledocholithiasis in Western countries usually results from stones originating in the gallbladder and migrating through the cystic duct. These \textit{secondary bile duct stones} are cholesterol stones in 75% and black pigment stones in 25% of patients. Cholesterol stones contain more than 70% cholesterol by weight, and variable amounts of bile salt and calcium. Over 90% of all cholesterol stones are radiolucent. Cholesterol stones are formed in the presence of cholesterol saturation, biliary stasis, and nucleating factors. Behavioral factors associated with cholesterol gallstones include nutrition, obesity, weight loss, and physical activity. Biologic factors linked to gallstones include increasing age, female sex and parity, serum lipid levels, and the Native American, Chilean, and Hispanic races.\textsuperscript{1} The formation of black pigment stones is associated with hemolytic disorders, cirrhosis, ileal resection, prolonged fasting, and total parenteral nutrition.\textsuperscript{3} These conditions lead to supersaturation of unconjugated bilirubin, which results in precipitation of bilirubinate with calcium and other anions in bile. The precipitated salt then becomes a nidus for black stone formation.

\textit{Primary bile duct stones}, on the other hand, form within the bile ducts and usually are of the brown pigment variety. These tend to be less than 20% cholesterol and higher in bilirubin content as compared with secondary stones. Unlike secondary stones, primary stones are associated with biliary stasis and bacteria.\textsuperscript{4} In fact, in the pathogenesis of brown pigment stones, bacterial enzymes unconjugate bilirubin glucuronide to form free bilirubin, which then precipitates with calcium to become the nidus for stone formation.\textsuperscript{5} Moreover, bacteria have been found in brown pigment stones by electron microscopy but not in black pigment stones.

Primary bile duct stones are more common in Asian populations, and these often are associated with \textit{primary intrahepatic stones} in this population.\textsuperscript{1} These intrahepatic stones usually are calcium bilirubinate and mixed stones and contain more cholesterol and less bilirubin than the extrahepatic bile duct pigmented stones. The pathogenesis of these intrahepatic stones appears to involve bile infection, biliary stasis, low-protein, low-fat diets and
malnutrition, and parasitic infections. However, the role of *Ascaris lumbricoides* and *Clonorchis sinensis* in the formation of intrahepatic stones is controversial. While these parasites are found in many geographic areas, primary intrahepatic stones are found mainly in Southeast Asia. Therefore, in addition to parasitic infections, other factors must play a role in the formation of these stones.¹

**Clinical Presentation and Natural History**

Asymptomatic bile duct stones may be found incidentally during evaluation of patients with suspected gallstones. In fact, 5% of common duct stones found during surgery may be unsuspected by preoperative findings and discovered only during intraoperative evaluation of the biliary tree. In one autopsy study of 615 patients over age 60, 1% were found to have bile duct stones.³ Patients with choledocholithiasis may present with biliary colic, bile duct obstruction, billirubinuria (or tea-colored urine), pruritus, acholic stools, and jaundice. However, the biliary obstruction usually is incomplete. There may be nausea and vomiting with intermittent or constant epigastric or right upper quadrant pain.⁶ The clinical course may be complicated by acute gallstone pancreatitis, cholangitis, or rarely, hepatic abscess. Infected patients may present with back pain, fever, hypotension, and mental status changes suggestive of cholangitis and ascending cholangitis. An asymptomatic state is also recognized.

CBD stones are covered by a bacterial biofilm of adherent quiescent bacteria residing in a hermetic environment. When stones cause obstruction of the ducts, cytokines released by epithelial cells activate these bacteria to the planktonic and virulent forms.¹ Therefore, bile duct obstruction secondary to stones often is accompanied by bacterial sepsis resulting from activation of the bacterial biofilm on these stones. Sepsis is much less likely to occur in the context of malignant obstruction without choledocholithiasis.

Although a majority of stones will pass spontaneously into the duodenum within hours, prolonged biliary obstruction can lead to biliary cirrhosis and portal hypertension. The average time for choledocholithiasis to lead to biliary cirrhosis is about 5 years, depending on the extent of obstruction.¹ Even with cirrhosis, however, the obstruction should be relieved because some reversal of portal hypertension and secondary biliary cirrhosis may be
Physical examination of patients with choledocholithiasis may be normal or may reveal jaundice, scleral icterus, and abdominal tenderness over the right upper quadrant without peritoneal signs. Early in the course, physical examination may not be very different from that of patients with cholecystitis. Severe tenderness may point to acute gallstone pancreatitis, whereas fever, hypotension, and confusion may suggest cholangitis.

Blood tests may reveal elevation of serum alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and bilirubin. Mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can be seen, whereas these are particularly abnormal in the situation of cholangitis. Although bilirubin and aminotransferase levels are high in 70% to 90% of patients at the onset of symptoms, almost all patients have elevation of ALP and GGT. Elevated amylase and lipase may suggest pancreatitis. Leukocytosis may be seen with cholangitis, pancreatitis, or associated acute cholecystitis. It is worth noting that laboratory evaluation of patients with bile duct stones can be normal repeatedly, and this should not dissuade further evaluation of patients suspected to harbor duct stones.

**Evaluation and Management**

The evaluation and treatment of choledocholithiasis are best discussed by considering the three clinical circumstances in which patients who may have bile duct stones are seen: prior to cholecystectomy, during cholecystectomy, or some time after cholecystectomy.

**PREOPERATIVE**

The diagnosis of choledocholithiasis cannot be made on the basis of history, physical examination, and laboratory investigations alone. Moreover, the distinction between the symptoms of bile duct stones and gallbladder stones is difficult. Increasing age, history of fever, cholangitis, and pancreatitis are risk factors for bile duct stones, whereas elevations of serum bilirubin, AST, or ALP are independent positive predictors.

Biochemical tests can be used as an initial screen to identify patients with high probability of CBD stones. ALP has the highest sensitivity (79.5%) for
CBD stones. Total bilirubin (TB) has the highest specificity (87.5%) and accuracy (84.1%) for CBD stones. A normal gamma-glutamyl transferase is excellent for exclusion of CBD stones (odds ratio of 3.2; negative predictive value [NPV] of 97.9%). For a patient with normal GGT, the likelihood of CBD stone is only 2.1%. An elevated GGT, ALP, TB, ALT, and AST has a sensitivity of 87.5%, compare to sensitivity of 96% for endoscopic retrograde cholangiopancreatography (ERCP).  

Transcutaneous ultrasound has been the traditional method of evaluating patients with biliary disease. It is highly accurate in identifying acute calculous cholecystitis and the presence of gallstones greater than 2 mm. Sensitivities and specificities of 48% to 100% and 64% to 100%, respectively, have been reported. However, the ability of transcutaneous ultrasound to establish the diagnosis of choledocholithiasis is only about 50%, varying from 30% to 90%. The role of ultrasound as a screening test for bile duct stones was evaluated prospectively by Gross and colleagues. Patients who were about to undergo ERCP were examined by right upper quadrant sonography to assess the size of the intra and extrahepatic ducts and for the presence or absence of bile duct stones. The findings were compared with ERCP, percutaneous transhepatic cholangiography, or surgical follow-up. Ultrasound was not found to be accurate in the diagnosis (sensitivity of 25%) or the exclusion (73% NPV) of choledocholithiasis.

Costi and colleagues studied the usefulness of the number and size of gallbladder stones for predicting asymptomatic choledocholithiasis. Ultrasound data of 300 consecutive patients undergoing laparoscopic cholecystectomy were analyzed. Patients were divided into two groups: those with multiple small (<5 mm) gallbladder stones or variable (≤5 mm and >5 mm) stones and those with large (>5 mm) stones only. The classification of stone size was confirmed by surgery in 95% of patients. Moreover, the presence of multiple small and variable gallbladder stones represented a risk factor for synchronous asymptomatic bile duct stones (9.5%) as compared with large stones only (2.5%). In another study, ultrasonography was found to have a positive predictive value (PPV) of 69% and an NPV of 78% for choledocholithiasis in patients suspected to have bile duct stones. This compared with serum transaminase tests having predictive values of 68% and 93%, respectively. In comparison to elevated serum transaminases and/or increased amylase levels, ultrasonographic evidence of CBD dilatation (>7
mm) has been described to be the best predictor of choledocholithiasis. Nonetheless, it is worth noting that almost half the patients with CBD stones do not have dilated ducts by ultrasonography, hence a negative study has limited value.

In order to predict the presence of bile duct stones more accurately, the combination of clinical, laboratory, and ultrasound risk factors has been used by several investigators. For patients over 55 years old with a bilirubin greater than 30 μmol/L (1.75 mg/dL) and a CBD more than 6 mm on ultrasound, the probability of a CBD stone is 72%. By multivariate logistic regression analysis, the combination of dilated CBD with evidence of stones by ultrasonography, clinical evidence of cholangitis, elevated aspartate transaminase and bilirubin, the likelihood of having stones in the bile duct was 99%. In the absence of all four of these findings, the probability of synchronous choledocholithiasis in patients with cholelithiasis was only 7%. Unfortunately, many patients present with only some of these findings, and the prediction of bile duct stones based on these criteria becomes difficult. Moreover, ultrasound sensitivity is in part operator-dependent and altered by bowel gas, making the findings inconsistent.

In 1968, ERCP was introduced as a diagnostic tool to aid in the management of biliary and pancreatic diseases. Five years later, with the development of endoscopic sphincterotomy, ERCP was transformed into a therapeutic modality. In 2009, 228,000 biliary endoscopies were performed in the United States, totaling $900 million in healthcare costs. Short of intraoperative examination, ERCP has long been considered the standard reference for the diagnosis of CBD stones. The specificity and sensitivity of ERCP were reported in 1982 by Frey and colleagues. ERCP was compared with findings on common duct exploration or cystic duct cholangiography in 72 patients and was found to have a sensitivity of 90%, specificity of 98%, and a 96% accuracy. Interestingly, the interval between performance of the procedure and operation was particularly important in patients with multiple small stones. Since small stones pass more readily from the gallbladder to the common duct and from the common duct to the duodenum, the longer the interval between ERCP and operation, the greater was the chance of discordant findings.

ERCP has the advantage of being both diagnostic and therapeutic for CBD stones (Figs 63-1 and 63-2). That is, after stones in the bile duct are
identified, endoscopic sphincterotomy and stone extraction can be performed at the same setting. ERCP stone extraction is successful 80% to 90% of the time using the techniques of sphincterotomy and balloon catheter or Dormia basket stone retrieval. The addition of mechanical, electrohydraulic, laser, or extracorporeal shockwave lithotripsy for large stones increases the success rate to over 95%.

FIGURE 63-1 Endoscopic retrograde cholangiopancreatography (ERCP) with distal common bile duct (CBD) stone prior to cholecystectomy.
FIGURE 63-2 Endoscopic retrograde cholangiopancreatography (ERCP) and common bile duct (CBD) stone extraction.

*Sphincterotomy* entails division of the papilla and sphincter muscles to widen the distal end of the CBD using a sphincterotome, a device consisting of a Teflon catheter with exposed cautery wire at the tip. The length of the intraduodenal part of the CBD limits the extent of the cut. *Balloon sphincteroplasty* is a sphincter-preserving alternative to sphincterotomy that uses a high-pressure hydrostatic balloon of either 6 or 8 mm diameter to dilate the papilla. One drawback of sphincteroplasty is the limited size of the papillary opening created as compared with sphincterotomy. Failure rates of 22% for stone extraction with balloon dilatation and the need for mechanical lithotripsy in 31% have been reported. Furthermore, sphincteroplasty has been associated with a pancreatitis rate of 19 times greater than the rate associated with sphincterotomy. A study evaluating the use of
sphincteroplasty, on the other hand, found that severe pancreatitis only occurred in 1 patient out of 63, whereas the successful stone extraction rate was 84%.28

Once the sphincter has been divided, most stones can be removed using a Dormia basket or a balloon catheter. The Dormia basket has better traction than the balloon and consequently is recommended for larger stones (>1 cm). The balloon catheter occludes the bile duct lumen after inflation and therefore is useful for removal of small stones and gravel. The catheter also can be inserted over a guidewire, making it useful for intrahepatic duct stones. Three situations that may lead to a difficult extraction are stone size greater than 1.5 cm, stone location proximal to a stricture, and multiple stones that are impacted. Alternative approaches to these situations include mechanical lithotripsy, electrohydraulic or laser lithotripsy, and extracorporeal shock wave lithotripsy. Mono-octanoin and methyl tertiary butyl ether (MTBE) have been used in the past to dissolve bile duct stones through nasobiliary drainage catheters or T-tubes. The practice largely has been abandoned because of high complication rates, poor results, and the technical difficulty of performing the dissolution.26

Mechanical lithotripsy is the most commonly used and simplest means of fragmenting large bile duct stones or when a significant discrepancy between the stone size and the diameter of the exit passage exists.29 A large, strong basket is used to trap the stone. The stone then is crushed against a metal sheath by applying tension to the wires by the use of a crank handle. Reimann and colleagues first described the technique in 1982, and since then, many variations in design have become available.30,31 When stones are extremely large, repeat application of the technique may be needed to further break the stone fragments and thus allow removal. Success rates between 80% and 90% have been reported for clearing the bile duct using the procedure.32-34 One retrospective study of 162 patients undergoing mechanical lithotripsy found that the probability of bile duct clearance was over 90% for stones less than 1 cm diameter versus 68% for stones greater than 2.8 cm diameter.35 Garg and colleagues presented data on 87 patients with stones greater than 1.5 cm that required mechanical lithotripsy.36 They analyzed various predictive factors, including size and number of stones, stone impaction, serum bilirubin, presence of cholangitis, and bile duct diameter, in relation to the success or failure of lithotripsy. Impaction of the stones in the bile duct
was found to be the only significant factor that predicted failure of mechanical lithotripsy and subsequent bile duct clearance. The composition of the stone also has been found to affect the success of stone removal. Soft stones, such as those found in Oriental cholangitis, are large but amenable to crushing, sometimes even with the Dormia basket. However, calcified stones are hard and resist mechanical crushing.

*Large-balloon dilatation* of the distal bile duct has been reported as a means of removing difficult bile duct stones after standard extraction has been unsuccessful. In a retrospective analysis, 58 patients who failed standard sphincterotomy and standard basket or balloon extraction underwent dilation with a 10- to 20-mm-diameter balloon (esophageal type) followed by standard basket or balloon extraction. The patients were divided into two groups: 18 patients with a tapered distal bile duct (group 1) and 40 patients with square, barrel-shaped, and/or large (>15 mm) stones (group 2). Stone clearance was successful in 89% of group 1 patients and 95% of group 2 patients. In the two patients in each group in whom extraction was not possible after dilatation alone, mechanical lithotripsy allowed for stone removal. Complication rates were high: 33% for group 1 and 7.5% for group 2, including mild pancreatitis (two patients), mild cholangitis (two patients), and bleeding (five patients). No bleeding required surgery. Large-balloon dilatation offers an alternative in managing difficult bile duct stones, and further studies are needed to establish its role as compared with other lithotripsy options.

The management of complicated situations of choledocholithiasis may require several procedures or several sessions of the same procedure for successful clearance of the CBD. In such situations, partial stone impaction may lead to biliary stasis and cholangitis. Along with the administration of broad-spectrum antibiotics to cover gram-negative and gram-positive bacteria, it is important to decompress the biliary tree with either a nasobiliary catheter or a biliary stent as a temporizing measure pending more definitive treatment. By doing this, serum bilirubin levels are allowed to decrease, and the rate of post-procedure cholangitis becomes similar to that after stone clearance. Interestingly, up to 30% of patients in whom a stent has been left in place for large stones have spontaneous disappearance of the stones, as noted on subsequent ERCP. This may be secondary to the frictional movement of stone against the stent or as a result of improved bile flow with dissolution effects. Furthermore, by adding oral ursodeoxycholic
acid to stent placement, 9 of 10 patients have been reported to become stone-free by this combination as compared with 0 of 40 with stent placement only.\textsuperscript{38} Long-term stent placement is an unconventional management option for patients with large, inextricable stones who are at high risk for surgical intervention, and should be used with caution. In a long-term follow-up study of 58 elderly patients, 40\% of patients treated with permanent stents for endoscopically irretrievable stones developed 34 complications in 23 patients, with cholangitis being the most frequent.\textsuperscript{39} At median follow-up of 36 months, 44 patients had died, 9 as a result of biliary-related causes. Hui and colleagues prospectively evaluated 36 high-risk patients with difficult CBD stones.\textsuperscript{40} Of these, 19 underwent stent placement, and 17 underwent complete stone clearance with electrohydraulic lithotripsy. The actuarial incidence of recurrent acute cholangitis was 8\% in the lithotripsy group versus 63\% in the stent group. The actuarial mortality also was higher in the stent group compared with the lithotripsy group, 74\% and 41\%, respectively.

Although ERCP has developed over the years as a relatively safe endoscopic diagnostic and therapeutic tool, there are well-defined, potentially severe, and life-threatening complications associated with it. The reported rates of complications vary widely in different studies, and this may be related in part to study design, with retrospective studies being prone to under-reporting. Furthermore, the complication rates may diverge depending on the patient mix in the study and may be influenced in part by the definitions used for these complications.\textsuperscript{22}

The mortality rate after diagnostic ERCP is about 0.2\%, and this rate is more than doubled by therapeutic interventions, to 0.5\%.\textsuperscript{21,22} Remember, these are essentially the same rates as for laparoscopic cholecystectomy. Cardiopulmonary complications are the leading cause of death and include cardiac arrhythmia, hypoventilation, and aspiration. These may be the result of premorbid conditions or related to medications used during sedation and analgesia. Other significant complications include perforations (0.3\%-0.6\%), bleeding related primarily to sphincterotomy (0.8\%-2\%), cholecystitis (0.2\%-0.5\%), and cholangitis (1\%). In a recent meta-analysis, prophylactic antibiotics were not found to be beneficial in reducing infectious complications of ERCP. Moreover, another study failed to show a decrease in the rate of cholangitis in patients with distal bile duct stones or biliary strictures receiving antibiotic prophylaxis.\textsuperscript{22}
Pancreatitis is the most common complication seen after ERCP. The consensus definition for ERCP-induced pancreatitis is new or worsened abdominal pain, serum amylase that is greater than three times the upper limits of normal at 24 hours post procedure, and a requirement of at least 2 days of hospitalization. Although the transient elevation of serum pancreatic enzyme levels is frequent, based on the consensus definition of ERCP pancreatitis, the expected rate of this complication is between 1% and 7%. Risk factors associated with ERCP-induced pancreatitis include a prior history of ERCP pancreatitis, nondilated biliary ducts, normal bilirubin, young age, female gender, and suspected sphincter of Oddi dysfunction. In fact, the risk of pancreatitis in women with normal bilirubin and suspected sphincter of Oddi dysfunction is 18%, compared with 1.1% for the low-risk patient. Moreover, one of five episodes of pancreatitis in this setting will be severe, requiring more than a 10-day hospital stay and/or resulting in necrosis, pseudocyst, abscess formation needing surgery or percutaneous drainage, or death. Since the highest rate of complications appears to exist in the group of patients that is least likely to benefit from ERCP, the most effective method of reducing post-ERCP pancreatitis would appear to be to avoidance of unnecessary ERCP.

Pharmacologic methods of pancreatitis prophylaxis have been attempted to reduce this complication after ERCP. Meta-analyses have suggested that somatostatin and gabexate are useful in reducing pancreatitis rates, but multicenter randomized, controlled trials have failed to confirm this. The use of nonionic contrast agents has not reduced the rate of pancreatitis. Glyceryl trinitrate (GTN) administered by both sublingual and transdermal routes has been shown to decrease post-ERCP pancreatitis in two placebo-controlled trials, supposedly by decreasing sphincter of Oddi pressure. Its hypotensive effects limit its use. The placement of pancreatic stents has been found to reduce the incidence of postbiliary sphincterotomy pancreatitis in patients suspected of sphincter of Oddi dysfunction.

Based on clinical, laboratory, and ultrasound criteria for CBD stones, up to 70% of patients may be found not to have duct stones at the time of preoperative ERCP. Given this, a large number of patients may be subjected to an unnecessary ERCP and suffer its risks and costs. Several methods have become available to diagnose the presence of bile duct stones accurately prior to having patients undergo ERCP or operative interventions. The most important of these are magnetic resonance
cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and computed tomography (CT).

Sensitivities of conventional CT for choledocholithiasis in the setting of suspected bile duct stones is 76% to 90%, whereas unenhanced helical CT has been shown to have a sensitivity of 88%, a specificity of 97%, and an accuracy of 94%. When compared with ERCP as the reference standard, CT without biliary contrast material showed poor concordance with ERCP (sensitivity 65% and specificity 84%) but compared better when oral biliary contrast material was given (sensitivity and specificity greater than 90%). CT with intravenous (IV) biliary contrast material in other studies has been found to have a sensitivity of 71% to 85% and a specificity of 88% to 95%. Patel and colleagues reported a comparison between noncontrast-enhanced helical CT and the reference standard of EUS and found that CT had both a sensitivity and a specificity of 83% for the detection of CBD dilatation in the setting of choledocholithiasis. However, when CT was evaluated for identifying duct stones, it had a sensitivity of only 22% and a specificity of 83%.

Since its introduction over a decade ago, the use of MRCP for the diagnosis of CBD stones has increased eightfold, while the use of ERCP as a diagnostic tool has decreased substantially. With sensitivities and specificities that approach those of ERCP, MRCP has emerged as a diagnostic alternative to ERCP for the detection and exclusion of choledocholithiasis. Additionally, economical and clinical cost analysis showed diagnostic MRCP is favorable over diagnostic ERCP in selected patients. Performed with $T_2$-weighted sequences, the biliary tract is seen as a bright structure with high-signal intensity without the use of contrast material, instrumentation, or ionizing radiation. Common duct stones are seen as low-signal-intensity filling defects surrounded by high-intensity bile. Improvements over the past decade have resulted in the ability to image the entire biliary tract in a single breath-hold of 20 seconds with a resolution that allows visualization of fourth-order intrahepatic bile ducts and small stones. Stones as small as 2 mm can be detected even in the absence of biliary dilatation. In one study of 97 patients, sensitivity of MRCP was 100% for stone diameters of 11 to 27 mm, 89% for stone diameters of 6 to 10 mm, and 71% for stone diameters of 3 to 5 mm. In this study, MRCP had a 91% sensitivity compared with 100% for ERCP, whereas both tests had a
specificity of 100%. Studies with state-of-the-art techniques have found sensitivities of 90% to 100% with specificities of 92% to 100%. In a prospective analysis by Ke and colleagues, 267 patients believed to have CBD stones were evaluated by MRCP and ERCP. MRCP was found to have a sensitivity of 100%, a specificity of 96%, and an NPV of 100%. Kejriwal and colleagues retrospectively examined patients with cholelithiasis who underwent MRCP for suspected choledocholithiasis. Patients were considered not to have clinically relevant common duct stones if they had a negative MRCP and did not present for readmission for choledocholithiasis after treatment of their cholelithiasis. MRCP was negative for bile duct stones in 74% of patients (60 of 81) and missed clinically relevant stones in two patients, resulting in a PPV of 95% and an NPV of 97%. With its ability to exclude bile duct stones, MRCP may allow the avoidance of unnecessary diagnostic ERCP. Demertines and colleagues found that even in patients with high and moderate risk of CBD stones based on laboratory findings, the performance of MRCP could have resulted in the avoidance of ERCP in 52% and 80% of patients, respectively.

One of the limitations of MRCP is that its resolution remains less than that of ERCP, and therefore it cannot detect small stones and crystals consistently. Claustrophobia also may influence the use of MRCP, and patients may need sedation or even general anesthesia for its performance. Patient obesity may diminish the quality of images, whereas morbid obesity, pacemakers, and aneurysm clips preclude entry into the scanner. Conversely, ERCP may be limited by an inability to access and cannulate the papilla and opacify the ductal system. Failed ERCP rates vary greatly among endoscopists, from 5% to 20%. Moreover, alterations in the gastrointestinal tract anatomy, such as a Billroth II gastrojejunostomy, may preclude access to the ampulla. In summary, MRCP offers a method of evaluating the biliary system for bile duct stones with sensitivities and specificities that approach those of ERCP in a manner that is noninvasive and avoids the risks and limitations of ERCP. Patients with a positive MRCP then may be considered for more invasive therapeutic procedures.

Another sensitive method of evaluating the biliary system for CBD stones is EUS. EUS has been shown to have a diagnostic accuracy of 95% for bile duct stones. With the high ultrasound frequencies used (7.5 and 12 MHz), EUS has a resolution of less than 1 mm, making it the best imaging technique
available for the extrahepatic biliary tract. Several studies have found EUS to be similar to ERCP in sensitivity and specificity for the evaluation of choledocholithiasis, with some showing ERCP to be better and others showing EUS to be better. Composed of ERCP, EUS is semi-invasive, with almost no procedure-related complications and a negligible failure rate. In fact, several series comprising over 1000 patients have reported no complications. In a prospective study by Buscarini and colleagues, 485 patients suspected to have choledocholithiasis based on clinical, laboratory, and ultrasound or CT findings underwent EUS. Positive EUS findings were confirmed by surgery or ERCP with sphincterotomy; negative findings were confirmed by clinical follow-up of at least 6 months. EUS findings were verified in 463 patients as follows: 237 true positive, 216 true negative, 2 false positive, and 4 false negative, and in 4 patients EUS was incomplete (sensitivity 98%, specificity 99%, PPV 99%, NPV 98%, accuracy 97%). No complications were noted in the study. EUS offers higher resolution than MRCP and therefore is better able to detect small stones. It is able to identify bile duct stones as well as microlithiasis and is able to detect pathology that is not seen by ERCP. EUS prior to performing invasive diagnostic or therapeutic techniques would lower the rate of procedure-related complications in patients suspected of having bile duct stones. Cost analysis of EUS followed by ERCP versus ERCP alone is also in favor of EUS as a pre-therapeutic procedure.

In patients for whom ERCP is not available, not possible secondary to anatomic considerations, or not successful, an alternative method of cholangiography and nonsurgical therapy is percutaneous transhepatic cholangiography (PTC) followed by transhepatic methods of stone removal. A needle is introduced into the intrahepatic bile ducts through the skin, and a cholangiogram is performed, followed by wire insertion and then a catheter over the wire for external biliary drainage and access to the biliary system. The method was introduced in Denmark in the 1970s and has been refined over the years with the addition of several therapeutic options. This technique is particularly useful for evaluating intrahepatic stones or other proximal bile duct disease. After diagnosis of bile duct stones, several therapeutic options are available through the percutaneous route. In 1981, the removal of an 8-mm CBD stone by percutaneous transhepatic technique was reported by Fernstrom and colleagues. In 1990, Stokes and colleagues,
from Boston, reported a series of 53 patients in whom surgery was contraindicated and ERCP unsuccessful.\textsuperscript{52} By inserting a modified Dormia basket via a percutaneous transhepatic route, stones were advanced whole or after fragmentation into the duodenum. Mono-octanoin or MTBE were used in 30 patients to reduce stone size or remove debris. Morbidity and mortality were 12\% and 4\%, with a success rate of 93\%. Transhepatic cholangioscopy and lithotripsy can be performed after PTC and dilatation of the intrahepatic channel with success rates of 90\% to 100\% and 5\% to 8\% complications.\textsuperscript{53} In a series of 12 patients with bile duct stones, PTC in combination with laser or electrohydraulic lithotripsy to deliver stone fragments into the duodenum was found to be successful in all the patients.\textsuperscript{54} In another series of 13 patients, laser lithotripsy was used with percutaneous cholangioscopy performed either transhepatically (12 patients) or through the T-tube track.\textsuperscript{55} Stone fragmentation was successful in 92\%, and stone clearance was possible in all patients. However, 11 patients required the addition of sphincterotomy (either by ERCP or by antegrade method with fluoroscopic monitoring) or stent insertion. Bleeding in two patients accounted for a 15\% severe complication rate. Percutaneous transhepatic papillary balloon dilatation was reported by a Japanese group for the management of choledocholithiasis.\textsuperscript{56} In the five patients in whom the method was used, bile duct stones were able to be pushed into the duodenum in all, with no complications or deaths. Ponchon and colleagues reported percutaneous choledochoscopy for stone extraction in 75 patients, with the transhepatic route used in 48 patients and T-tube tract used in 27 patients.\textsuperscript{57} Complete clearance of bile duct stones was accomplished in 69 patients (92\%).

**Role of Cholecystectomy Following CBD Stone Extraction.** After bile duct clearance is achieved by nonoperative methods, cholecystectomy generally is recommended in younger patients to decrease the risk of future cholecystitis and recurrent biliary colic. As many as 24\% of patients have been found to require cholecystectomy at follow-up after endoscopic papillotomy at an average of 14 months.\textsuperscript{58} Some authors have argued that sphincterotomy results in gallbladder stasis, bacterial overgrowth, and an increase in bile acids, and these may increase the risk of gallbladder cancer in 10 to 20 years.\textsuperscript{3} On the other hand, Dhiman and colleagues studied the changes in gallbladder emptying and lithogenicity of bile following endoscopic
Sphincterotomy in patients with choledochoolithiasis and gallbladder in situ. Sphincterotomy was found to decrease stasis of gallbladder bile, improve gallbladder emptying, and decrease the lithogenicity of bile as measured by prolongation of nucleation time. Meanwhile, there is much evidence to support leaving the gallbladder in situ after bile duct clearance in high-risk or elderly patients. In a study of 191 patients (median age 76 years) in whom the gallbladder was left in situ post-ERCP, only 10 patients (5%) required subsequent uneventful cholecystectomy. Twenty-six percent (49 patients) died during the review period from nonbiliary pathology. Kwon and colleagues followed 146 patients without elective cholecystectomy after endoscopic CBD stone removal for a period of 3 months or more to see if they could identify factors that predict subsequent gallbladder-related symptoms and need of cholecystectomy. Fifty-nine patients had cholelithiasis, whereas 87 patients had no gallbladder stones. During a mean follow-up of 24 months, seven patients (5%) underwent cholecystectomy, on average 18 months after ERCP as a result of acute cholecystitis (four patients), biliary pain (two patients), and acute pancreatitis (one patient). Nine patients (6%) died of causes unrelated to biliary disease. Interestingly, Cox regression analysis revealed that the need for subsequent cholecystectomy did not correlate with age, sex, presence of gallbladder stones, number of gallbladder stones, or underlying disease. Kullman and colleagues found that at a median observation time of 42 months, cholecystectomy was needed in 11% (13 patients) of 118 patients with a gallbladder in situ after ERCP bile duct clearance. Forty-nine patients (42%) died within 2 to 87 months after ERCP during the follow-up period. In another study of 33 elderly patients who were followed for an average of 42 months with gallbladder in situ after successful ERCP for choledochoolithiasis, 3% (one patient) required cholecystectomy for acute cholecystitis, and 6% (two patients) had mild right upper quadrant pain, whereas 91% remained asymptomatic. Over the course of the study, 30% of the patients died from nonbiliary causes.

The impact of gallbladder status on patient outcome after ESWL for complicated CBD stones was studied by a German group. One-hundred twenty patients with an average age of 68 years (range 28-86 years) were followed for 3 to 9 years (mean 4 years). Thirty-seven had their gallbladder in situ, 27 had had a cholecystectomy after ESWL, and 56 had already
undergone cholecystectomy prior to diagnosis of choledocholithiasis. During the follow-up period, 30% (36 patients) experienced biliary symptoms. However, there was no significant difference in the incidence of these symptoms between the three groups. Repeat ERCP revealed 28 cases of recurrent bile duct stones. Although not reaching statistical significance \((p = .077)\), the recurrences occurred more often in the cholecystectomy groups. Given the multiple studies supporting leaving the gallbladder in situ after CBD clearance, it seems reasonable to perform cholecystectomies on high-risk or elderly patients as needed rather than prophylactically following nonoperative treatment of bile duct stones.

**INTRAOPERATIVE**

When presenting to the operating room for cholecystectomy, patients may have CBD stones confirmed by preoperative studies (eg, ERCP, MRCP, or EUS), be suspected to have CBD stones by clinical presentation, laboratory values, or transabdominal ultrasound, or have no suspicion of bile duct stones. At the time of surgery, *intraoperative cholangiography* (IOC) is the diagnostic method used most often. Mirizzi first introduced IOC to open biliary surgery in the 1930s.\(^70\) With the universal acceptance of laparoscopic cholecystectomy, laparoscopic IOC has developed into a very useful method to evaluate the biliary tree. IOC and ECRP have similar sensitivity and specificity in CBD stone detection.\(^71\) The technique may be performed by injecting contrast material through a catheter introduced into the cystic duct via a variety of techniques.\(^72\) Cannulation rates with successful cholangiography range from 75 to 100%, and the use of fluoroscopy has become standard.\(^72,73\) The reported sensitivity, specificity, PPV, NPV, and accuracy for laparoscopic cholangiography are 80% to 90%, 76% to 97%, 67% to 90%, 90% to 98%, and 95%, respectively, and these are comparable with the values for open IOC.\(^70\) The rate of false positive IOC in a recent large review was found to be 0.8% (34 of 4209 patients).\(^74\)

Although approximately 10% to 15% of patients undergoing laparoscopic cholecystectomy harbor CBD stones, the need for routine IOC is a matter of much debate.\(^74\) In a large Medline literature review, Metcalfe and colleagues found a 4% rate of CBD stones in eight laparoscopic cholecystectomy trials in which routine IOC was performed on 4209 patients without suspected bile
duct stones preoperatively.\textsuperscript{72} This finding was felt to be consistent with previous reviews. On the other hand, in a total of 5179 patients without suspicion for bile duct stones who did not undergo IOC during laparoscopic cholecystectomy, 32 (0.6\%) proceeded to develop symptoms from residual bile duct stones. Extrapolating this data, it would seem that of the 4\% of patients with silent CBD stones at laparoscopic cholecystectomy, only 15\% go on to develop symptoms from retained stones. In other words, 167 IOCs would have to be performed during laparoscopic cholecystectomy in order to detect one CBD stone that would go on to cause symptoms in patients without preoperative evidence of duct stones. This would result in eight unnecessary bile duct explorations or ERCPs.\textsuperscript{72} It is possible that stones that are not manifested preoperatively are of the size that can pass spontaneously into the duodenum, never presenting with symptoms.

\textit{Intraoperative ultrasound} (IOUS) is a noninvasive way to evaluate the biliary system at the time of surgery. First introduced in the mid-1980s in the time of open cholecystectomy, laparoscopic IOUS came into use in the mid-1990s.\textsuperscript{70} Recent experience with laparoscopic IOUS has suggested that it is a very sensitive test for CBD stones and roughly equivalent to IOC in evaluating the biliary ductal system. Moreover, it lacks the potential of CBD injury that exists with placement of the cholangiography catheter during IOC and will not cause a false positive test owing to air introduced into the biliary tree.\textsuperscript{72} The use of laparoscopic IOUS has been limited, however, secondary to equipment availability and cost, as well as the expertise and experience required for its use. There appears to be a considerable learning curve associated with the use of laparoscopic IOUS.\textsuperscript{75,76}

Once the presence of CBD stones has been established at the time of surgery, there are several treatment options. Depending on local availability and expertise, these may include open or laparoscopic duct exploration and post-cholecystectomy nonoperative techniques such as ERCP or PTC. However, before embarking on a means of eradicating the biliary tree of stones, it is worth remembering that only 15\% of patients with silent bile duct stones at the time of cholecystectomy present with symptoms of retained stones.\textsuperscript{72} The natural history of choledocholithiasis was revisited in a prospective study by Collins and colleagues.\textsuperscript{77} Operative cholangiography was attempted in 997 patients undergoing laparoscopic cholecystectomy and was successful in 962 patients. Patients with cholangiogram-positive stones
were restudied in 48 and 72 hours and 6 weeks after laparoscopic cholecystectomy through a cystic duct cholangiocatheter left in the cystic duct at the time of surgery. Of the 962 patients, 46 (4.6%) had at least one filling defect but 12 had normal cholangiograms 48 hours later, giving a 26% possible false positive cholangiogram rate. At 6 weeks, a further 12 patients had a normal cholangiogram, giving a 26% spontaneous passage rate of bile duct stones. This spontaneous passage was not predictable by either the number or size of stones or the diameter of the bile duct. Only 2.2% of the total population (22 patients, or 48% of the patients with stones) required postoperative endoscopic retrograde cholangiopancreatographic retrieval of persistent common duct calculi. Thus a treatment decision based on the findings of IOC alone would have resulted in 52% of patients with positive findings undergoing unnecessary intervention.

The first surgical exploration of the CBD was done in 1890 by Ludwig Courvoisier, a Swiss surgeon who made an incision in the CBD and removed a gallstone. Prior to the development of laparoscopic cholecystectomy, patients found to have bile duct stones at surgery underwent open CBD exploration with greater than 90% successful duct clearance. ERCP was used for retained stones postoperatively or for patients who would not be able to tolerate extended general anesthesia. At the time of open cholecystectomy, the common duct is opened in the longitudinal direction so as to not compromise the blood supply to the duct. The bile duct is cleared of stones with the use of Fogarty balloons, saline irrigation, stone forceps, and scoops placed into the biliary tract through the opening. Choledochoscopy is particularly useful in evaluating the duct system during and after the clearance of residual stones and ruling out other ductal pathology. Moreover, a basket can be passed through the working channel of the scope and used under direct vision for stone removal. Although used commonly in the management of CBD stones in the era of open cholecystectomy, open bile duct exploration is used infrequently in the present age of minimally invasive surgery. In a series of 326 patients who underwent laparoscopic CBD exploration (LCBDE) for choledocholithiasis at the time of cholecystectomy, only five patients were converted to laparotomy and only two for open bile duct exploration and stone extraction.

Over a hundred years after Langenbuch performed the first open cholecystectomy in 1882, laparoscopic cholecystectomy was introduced and soon became the standard treatment of symptomatic gallstones. In the
early years after the development of laparoscopic cholecystectomy, LCBDE was used infrequently, and reliance on alternative methods of duct clearance was widespread. With increasing experience in laparoscopic techniques and the demand for single-procedure minimally invasive duct clearance, the use of LCBDE gained greater acceptance among experienced biliary surgeons. Since the development of the technique, thousands of successful LCBDEs have been reported in the literature, and success rates of duct clearance are between 80% and 90%, comparable with the open method of bile duct exploration. The morbidities range from 8% to 10% and are typical of laparoscopic procedures. Reported mortalities are from 0% to 2%.

The technique of LCBDE has been well described by Petelin. Access to the biliary system, after obtaining a cholangiogram, can be either transcystic or transductal using a choledochotomy. Use of the transcystic approach varies from 5% to 98%, depending on the series. With this method, the gallbladder is retracted toward the right hemidiaphragm, and if needed, the cystic duct is dilated with either over-the-wire mechanical or pneumatic dilators. The transductal approach is favored for stones greater than 6 mm in diameter, intrahepatic stones, cystic duct diameter less than 4 mm, and cystic duct entrance either posterior or distal. When using the transductal method, a choledochotomy is made on the anterior surface of the CBD with a scissors or scalpel and is limited to 1 cm or the size of the largest stone.

Once the biliary tree has been accessed, choledocholithotomy is performed using several different techniques and is guided by either fluoroscopy or choledochoscopy. Although separate monitors may be used with a choledochoscope, the use of a video mixer to place the laparoscopic and choledochoscopic images on the same screen is helpful. Newer choledochoscopes with 3-mm diameters even can be passed through the cystic duct. CBD clearance is started with irrigation, which allows the flushing of small, less than 3-mm stones and sludge. The administration of 1 to 2 mg IV glucagon allows relaxation of the sphincter of Oddi and facilitates the irrigation process. Fogarty-type balloons (4F) then can be inserted into the bile duct for retrograde extraction of stones with withdrawal of the inflated balloon. Stones also may be captured with a Dormia-type basket inserted directly through the cystic duct or choledochotomy or through the working port of the choledochoscope. Intraoperative electrohydraulic or laser lithotripsy is useful for large stones or stones that are impacted and not responsive to other methods. Care is needed, however, to avoid injury to the
duct by inaccurate application of the lithotripsy device.

If a choledochotomy is used to perform the LCBDE, a T-tube may be left in place for later study of the biliary system, decompression if the biliary tree was not cleared, or access to the biliary system for recurrent stones. On the other hand, laparoscopic suturing with 4-0 or 5-0 Vicryl can be done instead to close the choledochotomy primarily. A recent study found that hospital stay was shorter in a group of patients who underwent primary closure versus placement of a T-tube (5 vs 9 days). There does not appear to be an increase in the incidence of bile leak or peritonitis in patients undergoing primary closure. This further abrogates the complications of T-tubes, including dislodgement, bacteremia, fracture of the tube, and the possibility of bile leak and peritonitis at the time of T-tube removal. An alternative to T-tube placement is a stent placed in an antegrade fashion into the duct similar to an ERCP-placed stent. An alternative to a T-tube is a modified ureteral catheter placed through the cystic duct and brought out through the abdomen after closure of the choledochotomy. In a study of 30 patients undergoing placement of this modified catheter, no complications related to the catheter were found, and removal was possible at a median of 5 days as compared with 29 days when a T-tube was used.

If LCBDE is unsuccessful, a transcystic catheter may be inserted through the abdominal wall to decompress the biliary system and allow for postoperative cholangiography. If the catheter is further advanced into the duodenum, it can aid in bile duct cannulation at the time of postoperative ERCP. In addition to treating bile duct stones postoperatively following an incomplete laparoscopic duct clearance, the option of converting to an open duct exploration is also available to the operating surgeon.

There are several alternatives to laparoscopic or open duct exploration for bile duct stones encountered at the time of surgery. At the time of cholecystectomy, a transcystic stent may be placed over a wire antegrade through the sphincter of Oddi as initial treatment. This allows for decompression of the biliary tree and can be followed postoperatively by ERCP and sphincterotomy with stent removal. Another option is the use of intraoperative ERCP (IO-ERCP), allowing the same anesthetic to be used for both the cholecystectomy and the ERCP. In a study by Enochsson and colleagues, 592 patients underwent IOC during laparoscopic cholecystectomy. Thirty-four of these were subjected to IO-ERCP with a
100% CBD cannulation rate. The surgeon, while waiting for the endoscopist, introduced a thin guidewire into the IOC catheter and through the sphincter of Oddi into the duodenum. Bile duct clearance was possible in 94%, and a stent was left in place in the two patients with remaining stones. Operative time was prolonged by 1.5 hours as compared with laparoscopic cholecystectomy, but the length of hospitalization was not significantly longer for IO-ERCP patients. There were no cases of postoperative pancreatitis. In a report by Meyer and colleagues, 60 patients were treated with laparoscopic cholecystectomy and IO-ERCP for confirmed or suspected CBD stones.\(^8^4\) The mean operative time for laparoscopic cholecystectomy was 60 minutes (range 40-90 minutes), and general anesthesia was prolonged only 40 minutes (range 30-60 minutes) for performing the IO-ERCP, including the time needed for setting up the endoscopic equipment. The papilla could not be catheterized in two patients. In one, postoperative ERCP was possible, and in the second patient, a small stone passed spontaneously. In one patient, secondary to multiple calculi in CBD, open surgery was performed immediately after IO-ERCP. Final duct clearance was achieved in 100% of patients. The argument for using IO-ERCP versus postoperative ERCP is that the former allows the identification of anatomic problems (such as duodenal diverticulum) that could make later ERCP unsuccessful. Thus the surgeon has the option to convert to open bile duct exploration at the same anesthetic.\(^8^3\) If one chooses to use IO-ERCP, performing the cholecystectomy prior to the ERCP is important because this avoids endoscopy-induced small bowel distension from interfering with gallbladder visualization. Moreover, transcystic IOC at the time of cholecystectomy may avoid unnecessary ERCP if no stones are visualized by the cholangiogram.

**POSTOPERATIVE**

Patients presenting with CBD stones after cholecystectomy generally are treated with ERCP\(^7^3\) (Fig. 63-3). The noninvasive imaging techniques, such as ultrasound and MRI, are not different from those used preoperatively. If a T-tube (or other transabdominal drainage catheter) had been left in place at prior surgery, a cholangiogram can be obtained after surgery to establish the presence of bile duct stones. In situations in which ERCP is not possible or successful, other nonoperative methods can be used. For patients with T-tubes, percutaneous instrumentation under fluoroscopic guidance through the
T-tube tract can be used to remove bile duct stones. In one report, 23 of 25 patients underwent successful duct clearance through the T-tube tract for retained stones.\textsuperscript{86} A choledochoscope also may be inserted through the T-tube tract to allow for either laser or electrohydraulic lithotripsy and stone extractions.\textsuperscript{57} Other percutaneous transhepatic options described in the preoperative section of this chapter also may be used. Combinations and repeated techniques may be needed to achieve duct clearance. In the rare incidences where the biliary system cannot be cleared of stones nonoperatively, surgical duct exploration is considered, and the need for surgical drainage procedures must be addressed.

\textbf{FIGURE 63-3} Multiple retained stones after cholecystectomy, seen on endoscopic retrograde cholangiopancreatography (ERCP).
SURGICAL BILIARY DRAINAGE PROCEDURES

Surgical biliary drainage procedures must be considered in situations of multiple stones, incomplete removal of all stones, impacted, irremovable distal bile duct stones, markedly dilated CBD, distal bile duct obstruction from tumor or stricture, and reoccurrence after previous bile duct exploration. The methods of surgical drainage include transduodenal sphincteroplasty, choledochoduodenostomy (CDD), and choledochojejunostomy (CDJ).

Transduodenal sphincteroplasty (TDS) is useful in the management of choledocholithiasis when there is stone impaction in the ampulla of Vater, papillary stenosis, and multiple stones, particularly in the presence of a nondilated bile duct.\textsuperscript{87-89} The duodenum is Kocherized completely, and the ampulla is located by passing a biliary Fogarty catheter through the cystic duct into the duodenum. A longitudinal duodenotomy is made over the ampulla, and the entrance to the pancreatic duct is identified at the 4 o’clock position when possible. Intravenous secretin given at 0.2 g/kg over 1 minute sometimes is helpful in this identification. Absorbable sutures are placed on each side of the ampulla, and the sphincteroplasty is started at 11 o’clock and extended with sequential placement of sutures along the incision. After the opening is wide enough to fit a biliary dilator the size of the common duct, the last ampullary suture is placed at the apex to prevent a duodenal leak. The duodenotomy is then closed in the transverse direction to prevent duodenal stenosis, and a drain is left in place in the event that the duodenotomy leaks.

In a review by Suter and colleagues in 1994, of the 78 patients who underwent transduodenal sphincterotomy, 26 were operated on urgently.\textsuperscript{89} Forty-seven (60%) were jaundiced, 15 (19%) had pancreatitis, and 12 (15%) had cholangitis before surgery. Three patients died, one from pulmonary embolism, one from pulmonary sepsis, and one from multiorgan failure syndrome complicating preoperative necrotizing pancreatitis. Of the 30 patients (38%) with complications, 20 were directly related to the surgery and included 4 cases of bleeding not requiring transfusion, 17 instances of hyperamylasemia with 1 case of clinical pancreatitis, and 1 case of duodenal fistula that healed after conservative therapy. No deaths were noted that were directly attributable to the TDS. In an older review by Meyhoff, a 10% postoperative mortality was noted after TDS, with four patients developing fatal pancreatitis.\textsuperscript{87}

CDD was first performed by Riedel in 1888 in Europe.\textsuperscript{90} Unfortunately,
the patient died of anastomotic disruption secondary to a missed stone in the distal CBD. The first successful operation was performed by Sprengel in 1891. CDD is indicated in patients with recurrent stones requiring repeated interventions, impacted or giant stones, biliary sludge, and ampullary stenosis. The funnel syndrome in which a distal bile duct stenosis exists in the presence of primary CBD stones is one of the most classic indications for CDD. Most of the CBD stones in this situation are primary biliary stones forming as a result of biliary stasis. Any procedure done to remove only the stones has a temporary benefit if the stenosis is not addressed.

CDD can be performed either as an elective or an emergency operation, such as for cholangitis. The side-to-side anastomosis is the most commonly used technique, but an end-to-side is also an option. A CBD diameter of at least 1.2 cm is important in assessing the feasibility of CDD because this allows a wide enough stoma to ensure good biliary drainage and avert stenosis. The anastomosis is created in the most distal portion of the bile duct to decrease the chance of the well-described sump syndrome. The duodenum is Kocherized widely to allow for a tension-free anastomosis and the CBD is dissected completely along its distal anterior surface. A longitudinal duodenotomy is made close to the bile duct along the long axis of the duodenum, perpendicular to the choledochotomy. For a side-to-side anastomosis a 2-cm CBD incision is made along the long axis of the bile duct as close to the duodenum as possible. After performing a CBD exploration and clearing the duct of stones, a side-to-side single-layered anastomosis is made with absorbable monofilament suture, and a drain is placed for the possibility of an anastomotic leakage.

The morbidity and mortality rates associated with CDD are 23% and 3%, respectively. Mortality is most commonly from medical complications, such as pulmonary embolism, myocardial infarction (MI), or heart failure. Among the specific operative morbidities, cholangitis and sump syndrome are described most commonly.

The incidence of cholangitis ranges from 0% to 6% in the largest long-term follow-up series. Initially thought to be caused by ascending reflux of duodenal contents into the biliary tree, cholangitis is now believed to be the result of stenosis of the anastomotic stoma. A wide anastomosis avoids stasis and stone retention by allowing free flow of duodenal and biliary contents. Sump syndrome is caused by food and debris accumulating between the
stoma and the papilla of Vater. This leads to contamination of the large and small bile ducts with resulting recurrent cholangitis and even secondary biliary cirrhosis.\textsuperscript{90} Although the accumulation of debris in the blind segment of the bile duct may cause destruction of the stoma or cholangitis, some believe that the disease is caused by stenosis of the stoma. To avoid the problem, creating a stoma of at least 14 mm, along with placing the anastomosis near the duodenum, is important. Stomal patency is felt to be the most important factor for preventing both cholangitis and sump syndrome.\textsuperscript{90} Other reported complications of CDD include wound infection, anastomotic leak, and intra-abdominal abscess. Long-term studies reveal that 70\% to 80\% of patients are asymptomatic 5 years after surgery.\textsuperscript{90} In a review of 126 patients undergoing CDD after CBD exploration over a period of 19 years, Deutsch and colleagues reported a 4\% mortality rate, with all deaths occurring in patients over 70 years old.\textsuperscript{91} Morbidity included wound infections in 18 patients (14\%) and bile leak through a drain for over 2 weeks in 4 patients (3\%). Ninety-seven patients (94\%) were symptom-free at a follow-up of 1 to 19 years.

Ramirez and colleagues reported their experience with CDD and transduodenal sphincterotomy for the treatment of choledocholithiasis over a period of 10 years.\textsuperscript{92} Of the 591 patients who underwent choledochotomy for bile duct stones, 240 (40.6\%) were treated with primary closure over a T-tube, 126 (21.3\%) received primary closure over a T-tube along with a TDS, 216 (36.5\%) had a supraduodenal CDD, and 9 (1.5\%) had both a CDD and a TDS. CDD was performed when the bile duct was more than 12 mm in diameter, and TDS was used if a stone was impacted in the papilla and/or papillary stenosis was noted. Complications included six abdominal abscesses and three external biliary fistulas in the patients undergoing CDD, and four abscesses and two episodes of acute pancreatitis in the patients treated with TDS. There was no difference in mortality between the two groups, and after a mean follow-up of 5.6 years, 71.5\% of the CDD group and 75.2\% of the TDS group were asymptomatic. Symptoms noted in the remainder included dyspepsia, colicky pain, and episodes of cholangitis that resulted in reoperations for residual stones in nine patients, six from the CDD group and three from the TDS group. The same authors previously reported that of the patients who presented with symptoms after CDD and underwent endoscopy, no problems at the anastomosis were noted in patients who presented with dyspepsia, whereas 27\% of those with biliary colic had an
anastomotic stenosis or sump syndrome, and all the patients with cholangitis had stenosis and residual stones. On the other hand, in a comparison of 190 patients with CDD and 56 patients with TDS over a period of 10 years, Baker and colleagues found an overall mortality of approximately 5% in both groups. The morbidity rates were 11.6% for CDD and 21.4% for TDS. With a mean follow-up of 4.5 years, six patients (3.3%) in the CDD group presented with sump syndrome, cholangitis, or both, and three patients (5.7%) in the TDS group had cholangitis. In another report by the same authors, an elevated serum ALP level was noted in 22% of CDD patients and 3% of the TDS patients, whereas radiological studies showed that the CDD stoma admitted air and barium more often than the TDS stoma. Interestingly, neither the biochemical nor the radiological findings correlated with long-term symptomatic results after the two procedures.

An alternative to operative biliary drainage procedure to CDD is CDJ or hepaticojejunostomy, which can be performed with either a loop of jejunum or using a Roux-en-Y configuration. If a loop is used, a side-to-side (Braun) jejunojejunostomy is used to divert the flow of intestinal contents from the biliary tree. The authors prefer the Roux-en-Y reconstruction. The Roux-en-Y usually is brought retrocolic using a 40- to 60-cm afferent limb to protect against intestinal reflux and secondary cholangitis. In either case, an end-to-side CDJ is created using fine absorbable suture. The anastomosis can be decompressed using a T-tube if the remaining bile duct is long enough to allow one, or a transhepatic stent can be used if the remaining bile duct is short. As in the other methods of surgical drainage, a drain is left in place to guard against possible anastomotic leakage.

Gouma and colleagues reported their experience with 43 patients undergoing Roux-en-Y CDJ after complex clearance of the biliary tree for choledocholithiasis. No mortalities were reported and only one major complication. Moreover, 98% of the patients had good long-term results with no signs or symptoms related to biliary obstruction or cholangitis. A comparison of CDD and CDJ for choledocholithiasis was evaluated by a French group. One-hundred and thirty patients were included, of which 64 underwent CDD and 66 had a CDJ. No difference in morbidity or mortality was noted between the two groups. Of the 120 patients (58 CDD and 62 CDJ) available for a mean follow-up of 29 months, 107 were symptom free, 13 patients (6 CDD and 7 CDJ) experienced biliary symptoms suggestive of
cholangitis; 8 presented in the first postoperative year, and 5 presented in the second postoperative year. In the CDD group, the cholangitis was secondary to sump syndrome (three patients), anastomotic stricture (one patient), or unknown causes (two patients). Anastomotic strictures (three patients), residual intrahepatic stones (one patient), or unknown causes (three patients) were felt to be the cause of cholangitis in the CDJ group. The authors concluded that CDD is preferable given the similar outcomes because it is easier and faster to perform than CCJ and allows for easy endoscopic interventions if needed in the future. However, often the choice between the two operations is dictated by the anatomy and feasibility of creating a tension-free anastomosis. One controversy in performing surgical biliary anastomoses is the use of biliary stents. Earlier studies have argued that stents allow for decompression of the bile duct and decreased risk of bile leak, postoperative radiographic evaluation of the biliary tree, and reduced fibrotic narrowing of the anastomosis during early healing. Pitt and colleagues noted a higher success rate with the anastomosis stented for more than 1 month compared with those stented for less than 1 month or not stented at all. Others also have noted good results with the use of stents. However, Bismuth and colleagues showed that excellent results could be obtained in 86% of 123 patients undergoing stentless hepaticojejunostomy for benign biliary disorders. Pellegrini and colleagues found that stenting for more than 1 month postoperatively resulted in outcomes no different from anastomoses done without stents. The argument has been raised that stents cause an inflammatory reaction that may predispose to stenosis. DiFronzo and colleagues found that of the 97 patients having either a CDD (77%), CDJ (8%), hepaticoduodenostomy (1%), or hepaticojejunostomy (13%) without the use of stents, only one patient developed an anastomotic leak that resolved spontaneously within 1 week. In the mean follow-up period of 13 months, no postoperative strictures were noted. Meanwhile, Tocchi and colleagues presented their data on performing hepaticojejunostomy (48 patients), CDJ (34 patients), and intrahepatic cholangiojejunostomy (8 patients) without stents in 84 patients over a period of 15 years for benign biliary strictures. Excellent or good results were obtained in 83% of the patients. Anastomotic strictures occurred in 10 patients, 6 within 5 years and 4 at 62, 75, 85, and 96 months. By multivariate analysis, only postoperative complications and the degree of CBD dilatation proved to be significant
independent predictors of outcome. A bile duct dilatation of less than 15 mm was noted in 60% of patients with poor outcome. Although not reaching statistical significance, higher complications and restructures were noted in patients having a CDJ versus hepaticojejunostomy, and the authors changed their practice to performing only higher anastomosis during the study period for even low strictures. Peptic ulcers were noted in only 2.3% of the patients in the entire series, which is not higher than the normal population and does not appear to be related to diverting the flow of bile from the duodenum, as others have suggested.

Laparoscopic biliary drainage procedures have recently been reported for both benign and malignant biliary disease. A systemic review by Toumi et al. in 2011 reported on 89 patients from 19 separate reports in the literature. Many of these patients underwent laparoscopic biliary bypass combined with gastric bypass. The overall success rate was 98.9% with a morbidity rate of 12.3% and a mortality rate of 5.6%. Median follow-up was only 13 months. Longer-term data are needed as well as comparative studies with open surgical techniques.\textsuperscript{103}

Despite the proliferation of robotic-assisted surgery, its application to biliary surgery has remained rather limited. The literature thus far includes only two separate case reports and one small case series.\textsuperscript{104} One report describes robotic-assisted CBD exploration.\textsuperscript{105} The other report describes a robotic CDJ with an intracorporeal Roux limb construction.\textsuperscript{106}

Minimally invasive surgical drainage procedures are likely to become more widely used as experience increases and technology improves.

**SUMMARY**

The evaluation and treatment of choledocholithiasis has evolved over the last 100 years. As newer and less invasive techniques emerge, the surgeons will find a variety of options and many paths that can lead to the successful treatment of a patient with CBD stones. Evaluation and diagnosis may involve an examination and simple laboratory tests or evaluation of the biliary tree with MRCP, ERCP, or an IOC. Treatment may be endoscopic, percutaneous, open, laparoscopic, or a combination of techniques. Given the multiple alternatives available, sometimes it is difficult to decide on the right one for a particular patient. Frequently, the best path is the one the surgeon is most adept at or the one that local expertise can accomplish most safely.
Sometimes, however, the safest approach is a transfer to a center where multiple treatment options are available so that the treatment can be tailored to fit each individual situation.

Figures 63-4 and 63-5 show the treatments followed at our institution for preoperative and intraoperative suspected choledocholithiasis (at cholecystectomy).

**FIGURE 63-4** Algorithm for treatment of preoperative suspected choledocholithiasis.
**FIGURE 63-5** Algorithm for treatment of intraoperative suspected choledocholithiasis (at cholecystectomy).

**CHOLANGITIS**
Cholangitis is the most rapidly fatal complication of gallstones and occurs as a result of biliary tract bacterial infection in the setting of biliary tree obstruction. Mortality approaches 100% in patients who fail conservative therapy and do not undergo the needed drainage interventions. Early diagnosis and treatment are imperative for a successful outcome.

**Pathophysiology**

Although bile is normally sterile, when the biliary tree is obstructed or instrumented, such as by a stone, stricture, or endoprosthesis, bacteria are frequently cultured from the bile. Along with the sphincter of Oddi and the bacteriostatic properties of bile, bile flow is an important component of maintaining sterility. Bile duct obstruction results in decreased antibacterial defenses, allowing bacteria to gain access to the biliary tree. Although the route of infection is unclear, ascent from the duodenum or hematogenous seeding are felt to be the possible sources. Once colonization has occurred, stasis allows for exponential bacterial growth. As the biliary pressure rises with obstruction, bacteria and their endotoxins leak into the systemic circulation and cause the septicemia of cholangitis.

Patients with partial obstruction have a higher chance of developing cholangitis than those with complete obstruction, and bile duct stones are associated more often with cholangitis than neoplasms causing obstruction. In the United States, secondary choledocholithiasis is the most common cause of cholangitis. Primary bile duct stones are common in areas where recurrent pyogenic cholangiohepatitis (previously known as oriental cholangiohepatitis) is endemic, including Hong Kong and Southeast Asia. Other causes of cholangitis include obstructing periampullary tumors, tumors metastatic to the porta hepatis or peripancreatic lymph nodes, benign strictures, and primary sclerosing cholangitis. Biliary tract interventions may lead to post-procedural cholangitis, and rare cases of cholangitis may be caused by hemobilia, parasites, and congenital abnormalities of the biliary tree.

*Escherichia coli* (25%-50%), *Klebsiella* spp. (15%-20%), and *Enterobacteriaceae* (5%-10%) are the most common organisms cultured in cholangitis. Anaerobes may be present in 5% to 10% of patients. *Pseudomonas* spp. and skin and oral flora are associated with biliary tract
Interventions, whereas anaerobes are noted most commonly in the elderly after biliary surgery.\textsuperscript{11}

Clinical Presentation and Diagnosis

Charcot’s triad of fever, right upper quadrant pain, and jaundice are present in 50\% to 70\% of patients with cholangitis at presentation, with fever, abdominal pain, and jaundice occurring in 90\%, 70\%, and 60\% of patients, respectively. Hypotension (20\%) and altered mental status (30\%) are seen in septic patients and are known as Reynolds’s pentad when presenting in the setting of Charcot’s triad. Although peritonitis is uncommon, 65\% of patients have right upper quadrant tenderness.\textsuperscript{11} Laboratory and radiological studies are important for distinguishing cholangitis from other conditions such as acute cholecystitis, liver abscesses, and pancreatitis. Elevations of serum ALP, GGT, and bilirubin are typical. Mild increases in transaminases may be seen, whereas hyperamylasemia is found in up to 30\% of patients. A discussion of imaging studies for the evaluation of choledocholithiasis has been presented in the section on CBD stones. In a patient presenting with signs of cholangitis, the most widely used imaging modalities are ultrasound and CT scan. Ultrasound is highly accurate in diagnosing acute cholecystitis and identifying gallstones. However, its ability to establish the diagnosis of choledocholithiasis is only 50\%, varying from 30\% to 90\%.\textsuperscript{7,12} Although the presence of bile duct stones can be inferred by associated bile duct dilatation, a normal ultrasound without duct dilatation does not exclude choledocholithiasis or cholangitis.\textsuperscript{11,17} CT scan is better at determining the level of biliary tract obstruction and has a 94\% accuracy in diagnosing choledocholithiasis in the setting of suspected bile duct calculi.\textsuperscript{21} MRCP has sensitivities and specificities approaching ERCP in the diagnosis of bile duct stones and is useful in delineating biliary anatomy. However, its use in the setting of acute cholangitis is limited. ERCP is highly accurate in revealing the cause of biliary obstruction and at the same time allows for therapeutic intervention to occur at the same session.\textsuperscript{11} Nonetheless, given the well-defined life-threatening complications associated with ERCP and the availability of other noninvasive imaging techniques, ERCP should not be used solely as a diagnostic tool in the setting of acute cholangitis.\textsuperscript{11}
TREATMENT

Patients with cholangitis can become extremely ill in a short period of time, and rapid initiation of treatment can be lifesaving. Supportive measures are begun without delay and include fluid resuscitation, correction of electrolyte deficits and coagulopathy, and administration of analgesics. Empirical broad-spectrum antibiotics covering the common pathogens are started while blood cultures, and when available, bile cultures are sent. Aminoglycosides and ampicillin are associated with gram-negative resistance and nephrotoxicity and are no longer felt to be the ideal regimen. Newer effective therapies include combinations of extended-spectrum cephalosporins, extended-spectrum penicillins, metronidazole, and ampicillin; fluoroquinolones as single-agent or in combination with metronidazole; and ureidopenicillins alone or with metronidazole. Anaerobic coverage is felt to be more important in the elderly and those with biliary manipulations. Antibiotics usually are given for 7 to 10 days, even if biliary decompression has been accomplished during the interim. A retrospective study by van Lent and colleagues evaluated whether continuation of antibiotics is needed after biliary drainage is achieved and signs of inflammation have subsided. Eighty patients who were treated successfully for cholangitis with ERCP were included in the study and followed for 6 months. Forty-one patients received antibiotics for 3 days or less, 19 patients for 4 to 5 days, and 20 patients for more than 5 days. The three groups were well matched, and the rate of recurrent cholangitis (24%) was not different for the three groups. The authors felt that a 3-day duration of antibiotic therapy may be sufficient in treating cholangitis when adequate drainage has been achieved and fever is abating.

Drainage of the biliary tree is the mainstay of therapy for patients with acute cholangitis. However, the timing and route of biliary decompression vary depending on the response of antibiotics, the cause of the obstruction, and the presence of morbidities. Biliary sepsis will resolve in most patients with conservative therapy, allowing time for a detailed delineation of the biliary anatomy by noninvasive imaging (CT scan or MRI) to determine the cause and level of obstruction. However, urgent decompression is needed in the 10% to 15% of patients who fail to respond within 24 hours to supportive measures and antibiotic therapy. When biliary decompression is not achieved, liver abscesses are inevitable. Mortality approaches 100% in
patients who are not subjected to drainage interventions after failing conservative therapy.\textsuperscript{11}

The methods of relieving biliary tract obstruction include endoscopic, percutaneous transhepatic, and surgical drainage techniques. In a landmark article in 1992, ERCP was demonstrated in a randomized trial to be effective in controlling sepsis, and had a significantly lower mortality than surgical decompression (10\% mortality vs 32\%).\textsuperscript{110} More recent studies have confirmed this finding and further defined the benefits of ERCP over surgical decompression in the setting of cholangitis. In a study of 83 patients with acute cholangitis randomized to undergo either endoscopic or surgical decompression, the mortality was 10\% in the endoscopic arm versus 30\% in the surgical group.\textsuperscript{11} Meanwhile, in an evaluation of 65 patients undergoing endoscopic drainage versus 40 patients receiving traditional surgery for acute cholangitis, 5 operated patients and no individuals subjected to endoscopy died.\textsuperscript{111} In comparison with percutaneous drainage, ERCP also has been shown to have lower morbidity, shorter hospitalization, and higher definitive success rates.\textsuperscript{11} Sugiyama and colleagues found that in elderly patients (age 80 or older) with acute cholangitis, endoscopic drainage had lower morbidity (16.7\%) and mortality (5.6\%) than surgical (87.5\% and 25\%, respectively) or percutaneous drainage (36.4 and 9.1\%, respectively).\textsuperscript{112} With a success rate of 90\% to 98\% and low morbidity and mortality, ERCP with bile duct clearance is superior to the other methods and is the modality of choice for decompressing the biliary tree during acute cholangitis, particularly if caused by choledocholithiasis.\textsuperscript{11,109}

Various endoscopic treatment options are available from the placement of nasobiliary catheters or biliary stents to sphincterotomy and stone extraction. In patients who have responded to antibiotic therapy, sphincterotomy with bile duct clearance is preferred, whereas drainage catheters are used in those with ongoing sepsis and multiple large stones.\textsuperscript{109} In critically ill patients or in those with coagulopathy, concerns about bleeding and increased procedure times are associated with endoscopic sphincterotomy.

In comparing nasobiliary catheters with biliary stents for the treatment of acute cholangitis, a randomized study found both to be equally effective, but stents were more comfortable and avoided the risk of accidental removal.\textsuperscript{11}

Percutaneous transhepatic drainage is reserved for patients in whom the papilla is inaccessible or ERCP has failed and for those suspected of hilar
cholangiocarcinoma, hepatolithiasis, and intrasegmental cholangitis.\textsuperscript{11,109} Although successful in 90\% of patients with biliary obstruction, percutaneous drainage has higher rates of morbidity (30\%-80\%) and mortality (5\%-15\%) than endoscopic techniques. As with ERCP, coagulopathy must be corrected prior to the procedure.

Used for almost 100 years, open surgery for acute cholangitis is associated with mortality rates of up to 40\%.\textsuperscript{11} Surgery may be limited to choledochotomy, decompression, and T-tube insertion when performed for emergency situations. In patients who have undergone other methods of biliary drainage for the acute situations, surgery offers definitive treatment of the underlying disease and is associated with low mortality when performed electively after the initial treatment.

The need for cholecystectomy after CBD clearance in patients with cholelithiasis has been discussed in the section on choledocholithiasis. To prevent further biliary complications, some have advocated cholecystectomy for patients who are fit after the initial treatment of acute cholangitis. In nonrandomized and retrospective studies, the risk of developing subsequent biliary problems ranges from 4\% to 12\% in patients with CBD stones.\textsuperscript{11} In a study by Boerma and colleagues, 47\% of patients who were randomized to a wait-and-see approach after common duct clearance developed biliary symptoms compared with only 2\% of patients who were allocated to cholecystectomy within 6 weeks of the endoscopic procedure.\textsuperscript{113} Of the wait-and-see patients, 37\% eventually needed cholecystectomy. Targarona and colleagues randomized 98 elderly (mean age 80) patients with biliary symptoms to either open cholecystectomy with operative cholangiography and (if necessary) bile duct exploration (48 patients) or to endoscopic sphincterotomy alone (50 patients).\textsuperscript{114} There were no significant differences in immediate morbidity (23\% and 16\%) or mortality (4\% and 6\%) in the surgery versus endoscopic group. However, at a mean follow-up of 17 months, biliary symptoms recurred in three surgical patients, none of whom underwent repeat surgery, and in ten endoscopic patients, seven of whom had further biliary surgery. In conclusion, these studies suggest that patients with acute cholangitis should undergo elective cholecystectomy after bile duct clearance if they are able to tolerate an operation. Conversely, in Asian patients in whom bile duct stones may originate from intrahepatic stones, cholecystectomy may not prevent future biliary complications.\textsuperscript{11}
HEPATOLITHIASIS

Hepatolithiasis is a primary disease of the biliary ducts and is more refractory to surgical treatment than most other benign diseases of the biliary system. The disease is defined as stones in ducts proximal to the confluence of the hepatic ducts regardless of the presence of stones within the gallbladder or CBD. The relative incidence in Western countries is approximately 1%, whereas in Taiwan, South Korea, and China it has been reported to be 20%, 18%, and 40%, respectively. Originally felt to be common only in Southeast Asia and referred to as oriental cholangiohepatitis and Hong Kong disease, the widespread immigration of Asians to the United States has resulted in an increasing number of patients with hepatolithiasis presenting to American surgeons. Moreover, the North American experience includes a significant number of Caucasians and Latin Americans. This increasing incidence may be attributed to different etiologies such as primary sclerosing cholangitis, choledochal cysts, and iatrogenic biliary strictures.

The pathogenesis of primary hepatic stones was discussed earlier in the section on choledocholithiasis and appears to involve bile infection, biliary stasis, low-protein, low-fat diets and malnutrition, and parasitic infections. Brown pigment stones (calcium bilirubinate) are the most common stones and cholesterol stones are the second most common. Hepatolithiasis presents with recurrent pyogenic cholangitis and sepsis, complicated by parenchymal infection and liver abscesses, obstructive cholangiopathy, and subsequent parenchymal destruction and atrophy of involved lobe. The natural course of the disease may lead to the development of biliary cirrhosis, portal hypertension, and liver failure and is complicated by cholangiocarcinoma in about 10% of patients.

The diagnostic procedures used in establishing the diagnosis of hepatolithiasis include ultrasonography, CT scan, MRI, and direct (either endoscopic or percutaneous) cholangiography. Characterizing features include varying combinations of ductal dilatation, intrahepatic and extrahepatic bile duct stones, segmental ductal strictures, and lobar or segmental atrophy. In acute exacerbation, parenchymal or ductal contrast enhancement, abscess formation, or biliary obstruction may be noted.

The current management of hepatolithiasis is difficult and far from
satisfactory. The principles of treatment are centered on the decompression of abscesses, removal of stones, dealing with recurrences, and anticipating the development of malignancy. More than two-thirds of patients undergo multiple surgical procedures, and 10% ultimately require liver transplantation for liver failure. Initial biliary decompression usually can be achieved by endoscopic or percutaneous transhepatic drainage. The goal of definitive treatment is complete removal of all bile duct stones and elimination of bile stasis at the sites of intra- or extrahepatic strictures.

If the stones and strictures are located in a single segment or lobe of the liver, hepatic resection generally is recommended. Interestingly, there appears to be a predisposition for the left lobe of the liver. Resection is particularly important for patients with parenchymal atrophy and stricture of the intrahepatic ducts who may have concomitant cholangiocarcinoma. Even with resection, a significant number of patients will have recurrent disease. Kim and colleagues evaluated their experience with hepatectomy in 44 patients with hepatolithiasis by dividing them into two groups, those with intrahepatic biliary stricture and those without it. At a median follow-up of 65 months, the incidence of residual or recurrent stones was 36% for those with stricture and 11% for those without. The incidence of late cholangitis was higher in the stricture group (54%) versus the no-stricture group (6%), as was the initial failure rate (50% vs 31%, respectively). Intrahepatic stricture recurred in 46% of the stricture group versus none in the no-stricture group, with stricture reoccurrence seen at the primary site in two-thirds. Therefore, the importance of including the strictured duct in the hepatic resection is emphasized by this study.

Nevertheless, the number of patients in whom resection is feasible is limited secondary to the diffuse and multifocal nature of the disease. If stones are located predominantly in the extrahepatic ducts or at the primary convergence and there is minimal stenosis of the intrahepatic ducts, it may be possible to use endoscopic treatment. When stones or strictures are located at the secondary convergence or beyond, surgery and percutaneous transhepatic cholangioscopic lithotripsy have a complete stone clearance rate of 84% to 100% and 72% to 92%, respectively. However, the stone recurrence rate is high, ranging from 33% to 40%. Hepaticojejunostomy has been used in the past to prevent biliary-enteric regurgitation and to decrease stagnation of debris and calculi in the intrahepatic ducts. The use of hepaticojejunostomy is
controversial and is refuted by some authors, who claim that increased biliary complications occur in patients with hepaticojejunostomies in the setting of hepatolithiasis. However, adding a cutaneous stoma to the Roux limb of the hepaticojejunostomy creates an access point for entering the biliary system for treating future complications. A more appealing alternative to a stoma is the creation of a Hutson loop. This entails tacking the jejunal loop of the biliary-enteric anastomosis to the abdominal wall and clearly marking it with staples or a metal ring such that it can be easily accessed by percutaneous means. We believe that this option should be considered in every patient who undergoes surgery.

With the advent of biliary endoscopy and radiological intervention, percutaneous choledochoscopic removal of intrahepatic stones has been well established. Stones can be removed via cholangioscopic guidance with basket forceps or lithotripsy, and strictures can be dilated. In a study from Hong Kong, 79 patients with intrahepatic stones underwent percutaneous transhepatic choledochoscopy. The success rate was 76.8%, with a complication rate of 21.5%. Cholangitis occurred within 3 to 5 years in one-third of the patients after the procedure. Another study found that recurrent calculi are more common in the setting of bile duct strictures, and addressing the strictures is mandatory part of treatment. Meanwhile, one study of percutaneous transhepatic cholangioscopic lithotripsy reported a biliary clearance rate of 100%, with a mean of two sessions required and a complication rate of 6.7%. During the follow-up period of 1 to 127 months (mean 75 months), one recurrence was noted and treated by repeat choledochoscopy. Some authors have used percutaneous intracorporeal electrohydrolitic lithotripsy for hepatolithiasis. Using this technique, in a series of 53 patients, complete clearance of stones was achieved in 92%, and during a mean follow-up of 5 years, 9% had recurrent symptoms of biliary obstruction. Han and colleagues described the use of laparoscopy in the treatment of intrahepatic stones. A flexible choledochoscope, inserted through a choledochotomy, was used for stone removal in 12 patients, with a mean operating time of 288 minutes. Remnant stones were found in only one patient and removed by percutaneous choledochoscopy performed through the T-tube site. No cholangitis or recurrent stones were found at follow-up at 10 to 45 months.

The most recently documented North American experience describes
treating 42 patients between 1986 and 2005 at the University of Toronto. They operated on 17 patients (46%) for indications of lobar atrophy or stones confined to a single lobe. Patients who underwent an operation were found to have less need for reintervention. The incidence of cholangiocarcinoma was 12%, including patients who were diagnosed at initial presentation.

Although the evolution of this disease is unclear, it will likely continue to challenge us. With lessons learned from more common biliary pathologies and the application of novel technologies, we would anticipate better outcomes for our future patients.

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Benign conditions of the intrahepatic or extrahepatic bile ducts can range from focal or diffuse dilatations (choledochal cyst) to obstructive strictures of the biliary tree. Historically, choledochal cyst disease was considered a disease of childhood but is increasingly being recognized in adults. In the United States, benign biliary strictures most commonly occur as a result of injury after cholecystectomy but also occur in a number of diverse inflammatory conditions affecting the biliary tree. Both conditions represent significant clinical challenges where proper evaluation and management are paramount to prevent serious clinical sequelae.

**CHOLEDOCHAL CYST**

Choledochal cysts are focal or diffuse dilatations of the biliary tree, and aside from biliary atresia, they are the most common congenital abnormality of the biliary tree. Choledochal cysts can occur as single or multiple cysts throughout the extrahepatic or intrahepatic bile ducts. The cysts can
predispose patients to recurrent cholangitis or pancreatitis, choledocholithiasis, secondary biliary cirrhosis, biliary stricture, and malignancy.

The incidence of choledochal cysts varies significantly throughout the world. Choledochal cysts appear to be most common in Asian countries with an estimated incidence of 1 in 13,500; the incidence has been reported to be as high as 1 in 1000 in studies from Japan. In Western countries, choledochal cysts occur much less frequently, with reported rates that vary from 1 in 150,000 to 1 in 2 million live births. Biliary cysts are 4 times more common in women compared with men. Approximately 80% of choledochal cysts are diagnosed in children, and 20% of cases present in adults. There are a few case reports of choledochal cysts occurring within families, but generally, they do not have a recognized hereditary pattern.

**Classification**

The anatomy of choledochal cyst disease was first described by Vater in 1723, and in 1959, Alonso-Lej categorized 3 types of choledochal cysts. The classification system was revised by Todani and colleagues in 1977 to the 5 cyst categories that are in use today (Table 64-1). A similar classification has been proposed based on bile duct cholangiographic appearance.

<p>| TABLE 64-1: ALONSO-LEJ/TODANI MODIFICATION OF THE CLASSIFICATION OF CHOLEDОCHAL CYSTS |</p>
<table>
<thead>
<tr>
<th>Type I</th>
<th>Classic cyst type characterized by cystic dilatation of the common bile duct; most common, comprising 50%-80% of all biliary cysts; subdivided into IA (cystic), IB (fusiform), and IC (saccular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed type I and II</td>
<td>Fusiform dilation of the extrahepatic biliary tree in combination with a separate diverticulum, midportion of the common bile duct, with cystic duct entering in the right of the diverticulum, comprising 1%</td>
</tr>
<tr>
<td>Type II</td>
<td>Simple diverticulum of the extrahepatic biliary tree, comprising 2%-3% of all cysts; located proximal to the duodenum</td>
</tr>
<tr>
<td>Type III</td>
<td>Cystic dilatation of the intraduodenal portion of the extrahepatic common bile duct; also known as a choledochocele; comprising approximately &lt;10%</td>
</tr>
<tr>
<td>Type IV</td>
<td>Involve multiple cysts of the intrahepatic and extrahepatic biliary tree; subdivided into type IVA (both intrahepatic and extrahepatic cysts) and IVB (multiple extrahepatic cysts without intrahepatic involvement); type IVA is the second most common type of biliary cyst, comprising 30%-40%; type IVB comprises &lt;5%</td>
</tr>
<tr>
<td>Type V</td>
<td>Isolated intrahepatic biliary cystic disease, also known as Caroli disease; associated with periportal fibrosis or cirrhosis; can be multilobar or confined to a single lobe, comprising &lt;10%</td>
</tr>
</tbody>
</table>

Traditionally, the classic and most common choledochal cyst is type I disease: (A) cystic (Fig. 64-1A), (B) saccular, or (C) fusiform dilatation of the extrahepatic biliary tree. Type II cysts are simple diverticula of the common bile duct, which are usually extrahepatic, supraduodenal, and saccular (Fig. 64-1B). A rare combination of type I cystic dilatation and type II diverticulum was reported in a few cases representing a mixed type. A type III cyst, also known as choledochocele, is a focal cystic dilatation of the most
distal segment of the bile duct (Fig. 64-1C). Manning and colleagues\textsuperscript{7} described 2 anatomic variations of intraduodenal choledochocele. The most frequent variety is with the common bile duct and main pancreatic duct entering into the choledochocele separately. The second variety of intraduodenal choledochocele is essentially a diverticulum off the common bile duct at the level of the ampulla of Vater, with the pancreatic duct entering the end of the common bile duct in the usual location. Multiple dilatations of the intrahepatic and extrahepatic biliary tree are known as type IV cysts divided into type IVa and type IVb. Type IVa represents fusiform extrahepatic and intrahepatic cysts (Fig. 64-1D). Type IVb consists of multiple extrahepatic cysts (Fig. 64-1E). Type V cyst, Caroli disease, is confined to the entire liver or a solitary lobe, usually on the left (Fig. 64-1F).\textsuperscript{2,3} This disease may be associated with periportal fibrosis and cirrhosis, leading to subsequent hepatosplenomegaly and portal hypertension.

\textbf{FIGURE 64-1} Illustrations of the Todani classification of choledochal cysts.
A. Type IA. B. Type II. C. Type III. D. Type IVA. E. Type IVB. F. Type V.

While Todani’s 1977 schema is the most widely accepted classification, it is not without controversy. Some have argued that the term “choledochal cyst” should refer to only type I and IV cysts (which compose over 90% of biliary cysts). This proposal is based on current understanding of pathogenesis, treatment, malignancy risk, and natural history, which vary substantially with type I and IV cysts versus type II, III, or V cysts. A review from Indiana University questioned whether choledochoceles were truly choledochal cysts. They reviewed 146 patients with choledochal cysts and identified 28 patients with choledochoceles. They concluded that classifications of choledochal cysts should not include choledochoceles because they differ from choledochal cysts with respect to age, sex, presentation, pancreatic ductal anatomy, and management.

Pathogenesis

The cause of choledochal cysts is unknown. While there have been reports of acquired cysts in the literature, most are congenital in nature. There may be multiple mechanisms involved in the creation of biliary cysts, and several theories have been proposed.

The high incidence of biliary cysts in Asia suggests a role for either genetic or environmental factors. The first theory pertains primarily to the pathogenesis of Caroli disease and is related to a defect in maturation with ductal plate malformation. This defect can be either sporadic or inherited, with both autosomal recessive and, rarely, autosomal dominant inheritance patterns seen in families. Ductal plates describe the development of intrahepatic liver progenitor cells that are in contact with the mesenchyme of the portal vein and are then remodeled into mature ducts. Defective bile duct plate remodeling during embryogenesis results in inflammation and ulceration of biliary epithelium into larger bile ducts. These ducts then become segmentally dilated in a focal, lobar, or multilobar distribution.

The second theory for the etiology of choledochal cyst formation is that bile duct obstruction or distention in the prenatal or neonatal periods may contribute to biliary cyst formation. The obstruction may be secondary to a stricture, web, or sphincter of Oddi dysfunction. With distal biliary
obstruction, there is pancreatic juice reflux into the biliary tree resulting in chronic inflammation and increased bile duct pressure, leading to dilatation.\textsuperscript{11} In animal models, bile duct ligation in neonates leads to cyst formation; in contrast, bile duct ligation in adult animals results in gallbladder distention.\textsuperscript{12} In addition, there are case reports of a congenital web at the lower end of the common bile duct and antenatal choledochal cyst with distal common bile duct formation.\textsuperscript{13}

The most common proposed theory for choledochal cyst formation is related to pancreaticobiliary maljunction.\textsuperscript{14} Pancreaticobiliary maljunction is defined as an extramural junction of the pancreatic and biliary ducts in the duodenum beyond the intramural sphincter function and is characterized by a long common channel. On average, patients with this anomaly have a common channel that is 1.86 cm, compared with 0.46 cm in patients with a normal junction.\textsuperscript{15} In the literature, pancreaticobiliary maljunction has been reported in 90\% of patients with choledochal cyst disease (Fig. 64-2).\textsuperscript{16} Pancreaticobiliary maljunction is also thought to be a significant risk factor for the development of cholangiocarcinoma in the biliary cyst,\textsuperscript{17} as well as the development of gallbladder cancer. Several investigators have speculated on the embryologic etiology of pancreaticobiliary maljunction, hypothesizing that the development of pancreaticobiliary maljunction is a result of an arrest in the migration of the choledochopancreatic junction into the duodenal wall.\textsuperscript{18}
Because of the long common channel, patients with pancreaticobiliary maljunction may have increased reflux of pancreatic juice into the biliary tree, since the ductal junction lies outside the sphincter of Oddi and cannot prevent the mixing of bile and pancreatic juices. The mixed juices then have the potential of stagnating in the ducts or gallbladder, resulting in a cycle of inflammation, activation of proteolytic enzymes, theoretical biliary epithelial damage, alterations in bile composition, and ductal distention. It is thought that a combination of these factors contributes to the development of malignancy within the choledochal cyst or gallbladder. Elevated sphincter of Oddi pressures have also been documented in patients with pancreaticobiliary maljunction, resulting in more reflux.
On pathology, choledochal cysts have variable microscopic features, with appearance ranging from normal bile duct mucosa to carcinoma. In children, the classic histologic appearance is a thick and dense fibrotic cyst wall with evidence of acute or chronic inflammation. In adults, common findings are inflammation, erosions, sparseness of mucin glands, and metaplasia.\textsuperscript{1,22} Type III cysts are most often lined by duodenal mucosa, although they sometimes are lined by bile duct epithelium.\textsuperscript{22} When malignancy is present, it is most commonly found along the posterior cyst wall.

**Presentation**

Choledochal cyst disease can present with a vast spectrum of symptoms. The classic triad of presentation of a choledochal cyst is a female child with jaundice, abdominal pain, and right upper quadrant abdominal mass. This triad is found in only a minority of children at the time of presentation. Infants commonly present with elevated conjugated bilirubin (80%), failure to thrive, or an abdominal mass (30%). An abdominal mass becomes less common with increasing age and is rarely appreciated in adults. In adults, abdominal pain and recurrent cholangitis are the most common presentations.\textsuperscript{23} The abdominal pain usually mimics that of calculous cholecystitis, and many patients do have gallstones either in the cyst or in the gallbladder. Almost 38% of adult patients have had a cholecystectomy before the diagnosis of a choledochal cyst because of right upper quadrant pain, which was attributed to gallbladder disease.\textsuperscript{24} Intermittent jaundice and recurrent cholangitis are also common, as is pancreatitis (30%), especially in patients with a type III cyst (choledochocele).\textsuperscript{1,9,25} Rarely, choledochal cysts will present as intraperitoneal rupture or bleeding due to erosion into adjacent vessels.

**Diagnosis**

The diagnosis of a choledochal cyst requires a high level of suspicion. Unless choledochal cyst is considered in the differential diagnosis in patients with ductal dilation, type I cysts may go undiagnosed. Patients with biliary obstruction, either acutely or chronically, may also have biliary dilatation that can mimic a type I cyst. In contrast to a type I cyst, an obstructing lesion will
often cause elevated alkaline phosphatase and bilirubin, as well as improvement in biliary dilation after appropriate treatment. The presence of pancreaticobiliary maljunction in uncertain cases can also be helpful in making the diagnosis of a type I cyst versus a biliary obstruction.

Ultrasonography is the most common first-line imaging tool and was used in 93% of the pediatric population and 72% of the adult patients in the Johns Hopkins series. While ultrasound is the standard for antenatal and childhood diagnosis, computed tomography (CT) scan may be more appropriate in adult patients, in whom the differential diagnosis is broader. Important considerations on CT scan (Fig. 64-3) include assessing the hepatobiliary and pancreatic anatomy, with evaluation for possible biliary malignancy, metastatic disease, and vascular encasement.
Ultimately, when choledochal cyst disease is suspected on imaging, visualization of the pancreatic, intrahepatic, and extrahepatic ductal anatomy is required. Magnetic resonance cholangiopancreatography (MRCP) has become the noninvasive procedure of choice for the diagnosis of choledochal cyst. As quality of MRCP has improved, many surgeons now consider MRCP the only imaging technique needed for diagnosis and operative planning. Park and colleagues\textsuperscript{26} retrospectively reviewed 72 adult patients who underwent both MRCP and endoscopic retrograde cholangiopancreatography (ERCP) and found that when compared with ERCP, MRCP was accurate 100% of the time with type IVB and V cysts.

Cholangiography had previously been considered the gold standard for diagnosis of choledochal cysts but now only is necessary as primarily a therapeutic procedure to place stents to relieve jaundice or cholangitis or to obtain brushings for cytology. Cholangiography can demonstrate areas of cystic dilatation and the presence of stones and exclude complete obstruction of the bile duct (Fig. 64-4). It is also effective in demonstrating the presence of pancreaticobiliary maljunction. Percutaneous transhepatic cholangiography (PTC) or ERCP is typically performed on adults and larger children. In small children, ERCP is not the ideal tool because it involves the use of general anesthesia; can lead to pancreatitis; and may not define the very proximal biliary anatomy, which tends to be abnormal. Therefore, in children, intraoperative cholangiography may be used. In patients with type I or type IV cysts that extend to the hepatic bifurcation, PTC allows for the placement of 1 or 2 transhepatic biliary catheters, which may be helpful to facilitate complete resection and biliary reconstruction (Fig. 64-5). To decrease the high risk of pancreatitis in patients with pancreaticobiliary maljunction and a long channel, it is important to avoid placing the stent through the ampulla while performing PTC.
FIGURE 64-4 Percutaneous cholangiogram via the right hepatic duct. A large type I choledochal cyst is seen. Note the anomalous choledochopancreatic duct junction.
FIGURE 64-5  Type IVA choledochal cyst. Bilateral percutaneous biliary drainage catheters (arrows) were placed in this patient, who had extensive intrahepatic biliary duct dilatation (arrowheads) and a huge extrahepatic choledochal cyst (curved arrow). Note that the biliary catheters exit the cyst and enter the duodenum (open arrows).

**Management**

Once the diagnosis of choledochal cyst is made and the patient’s biliary anatomy is delineated through preoperative imaging, several important clinical considerations must be taken into account. If a patient presents with pancreatitis or cholangitis, these problems must be treated supportively prior to considering definitive operative management of the biliary cyst. Because of the extensive sludge or stones that may be present within choledochal
cysts and the high incidence of pancreaticobiliary maljunction, these patients are at especially high risk for pancreatitis. Furthermore, there is a risk of pancreatitis during ERCP with ampullary stent placement.

Another important clinical consideration in patients with choledochal cysts is the presence of malignancy. Adenocarcinoma comprises 73% to 84% of malignancy associated with choledochal cysts, and additional histologic subtypes include anaplastic carcinoma (10%), undifferentiated cancer (5%-7%), squamous cell carcinoma (5%), and other types such as bile duct sarcoma. The incidence of cholangiocarcinoma with biliary cysts varies with patient age and cyst type. The lifetime risk of associated cholangiocarcinoma is 6% to 30% in several studies, and importantly, the rate of malignancy increases with age. Patients discovered in their 20s have only a 2.3% risk of concomitant malignancy, but this risk increases to 14.6% for patients with choledochal cysts discovered in their 30s and 40s. In older untreated patients, the reported incidence of cholangiocarcinoma is as high as 75%. In a review examining the occurrence of malignancy in 5780 patients with choledochal cyst, the overall incidence of biliary tract cancer was 7.5%. The incidence in children (age 0-18 years) was low (0.4%), with increased rates in those older than 18 years (11%). The incidence steadily increased with age up to 38% in patients older than 60 years. Among patients who develop malignancy, 70% arise as cholangiocarcinoma within the cyst wall and approximately 24% arise as gallbladder cancer. Type I and IV cysts have a higher risk of cancer, whereas cancer is rare in type II and III cysts. In type III cysts, cancer risk may be limited to those choledochoceles lined by biliary and not duodenal epithelium. Caroli disease also carries a risk (approximately 7%) of cholangiocarcinoma. Most patients with Caroli disease, however, will present first with compromised liver function or cholangitis before developing malignancy.

The Johns Hopkins series included 92 choledochal cyst patients, with 8 of the patients being diagnosed with cancer at the time of surgery or in follow-up. Every cyst type, except types II and III, was involved with cancer. None of the patients who had a complete cyst excision developed cancer after a mean of 10 years of follow-up. However, this population was still at a greater risk of malignancy than the general population. Malignancy may develop with incompletely resected cysts, at the anastomotic site, or in residual cyst left within the pancreas.
Speculated etiologic factors in carcinogenesis associated with biliary cysts include bile stasis, reflux of pancreatic juice mixed with bile, superinfection, or inflammation.\textsuperscript{29,30} Cholangiocarcinoma in choledochal cysts is strongly linked to patients with pancreaticobiliary maljunction.\textsuperscript{17} There is strong pathologic evidence of a hyperplasia-dysplasia-carcinoma sequence of carcinogenesis in patients with pancreaticobiliary maljunction. While the exact pathways have yet to be elucidated, cells with hyperplasia in patients with pancreaticobiliary maljunction have elevated expression of cellular proliferation markers, including cyclooxygenase-2 and vascular epithelial growth factor.\textsuperscript{31} On a molecular level, hyperplastic cells also have a high incidence of $K\text{-}ras$ mutations (13%-63%),\textsuperscript{32,33} whereas dysplastic cells frequently have microsatellite instability (60%)\textsuperscript{34} and cancerous lesions often have overexpression of cyclin D1\textsuperscript{35} and $p53$ mutations.\textsuperscript{36} Prophylactic cholecystectomy is also advised in all patients with either pancreaticobiliary maljunction or choledochal cyst.

In addition to the continued risk of cancer after excision, the most frequent long-term complication after biliary reconstruction is postoperative biliary stricture at the site of the anastomosis (approximately 25%).\textsuperscript{37} Therefore, long-term follow-up should include surveying patients for the development of an anastomotic stricture. Significant elevations in serum alkaline phosphatase levels merit further investigation and treatment to prevent long-term complications from postoperative biliary strictures.

Unfortunately, current methods for screening for malignancy within a choledochal cyst have not proved effective, and therefore, expectant management cannot be advised for most patients. Intraductal ultrasound and cytologic brushings of the cyst wall show promise for potentially detecting malignancy. Patients with choledochal cysts who are poor candidates for or who refuse biliary reconstructive surgery may be candidates for lesser interventions to treat symptoms caused by gallstones or sludge, such as cholecystectomy or endoscopic treatment.

**OPERATIVE MANAGEMENT**

Historically, choledochal cysts were managed with biliary-enteric drainage via cyst enterostomy. Recognition of an increased risk of bile duct and gallbladder cancer at an average of 10 years\textsuperscript{28} after enteric drainage has
changed the recommended management to complete cyst excision. The current treatment of choice is surgical excision, because it is well documented to lead to a decrease in the rate of malignancy from 16% to less than 1%.25,29 The main goal of management is therefore to prevent malignant degeneration of the cyst via surgical excision. In newly diagnosed adult patients with biliary cysts, the possibility of an existing cancer needs to be considered.

The operative management of choledochal cysts should first consist of careful exploration of the patient. Upon entry to the abdomen via a midline incision, the initial step should be searching for possible metastatic disease. Once metastatic disease has been excluded, management of the choledochal cyst consists of cholecystectomy and complete cyst excision. If possible, excision should include all remnants of the cyst. Because of the extensive fibrosis that may be present, complete excision of the cyst can be technically challenging. Following cholecystectomy and choledochal cyst excision, the bile duct is reconstructed. Standard methods to reconnect the bile duct include hepaticojejunostomy or hepaticoduodenostomy, although Roux-en-Y hepaticojejunostomy is by far the most commonly used technique.37

Enteric interposition grafts have been proposed as an option due to theoretical restoration of physiologic bile flow. Both jejunal interposition grafts and appendiceal interposition grafts between the duodenum and bile duct have been reported in the pediatric surgery literature. The value of these techniques, however, has been questioned because of graft dysfunction from stenosis and kinking.38

Successful resection and biliary reconstruction with type I and type II choledochal cysts have also been reported using laparoscopic techniques, particularly in children. A review of 35 adult patients with choledochal cysts that were resected laparoscopically was done, which showed a 0% mortality, 8.5% conversion rate, and 14.8% reoperation rate.39 In another series by Senthilnathan et al,40 110 patients underwent laparoscopic resection and reconstruction of type I or type IVA choledochal cysts. The overall mortality was 1%, reoperative rate was 2%, and morbidity was 10%. Thus, this study demonstrated that laparoscopic surgery for choledochal cysts is feasible, safe, and even advantageous.40 While the choice of performing these procedures via an open or laparoscopic approach should be a matter of preference and technical ability of the surgeon, it is important that the procedure not be compromised by the use of laparoscopy.
**Type I Cysts.** The surgical approach recommended for type I cysts is complete cyst excision with Roux-en-Y hepaticojejunostomy reconstruction. The technical aspects of this operation involve mobilization of the hepatic flexure and wide Kocher maneuver to expose the distal portion of the cyst that lies posterior to the duodenal wall (Fig. 64-6A). After the cyst has been exposed, the gallbladder, which usually arises from the mid-portion of the choledochal cyst, should be dissected away from the hepatic bed (Fig. 64-6B). The procedure then focuses on the distal portion of the choledochal cyst (Fig. 64-6C). Type IB (fusiform) cysts are particularly prone to extend distally within the common bile duct as it enters the dorsal aspect of the pancreas. The goal is then to excise the intrapancreatic portion of the cyst without injuring the pancreatic duct or the long common channel. Resection of the pancreatic head can usually be avoided unless there is documented malignancy. The distal portion of the cyst is encircled and transected as it enters into the pancreas and then reflected cephalad (Fig. 64-6D). This allows posterior dissection and identification of the portal vein and hepatic artery. The dissection may be facilitated by the presence of a preoperatively placed transhepatic stent. The dissection is continued until the most proximal portion of the duct at the hilum. The cyst is then resected at the hepatic duct confluence or more proximally if the cyst extends into the individual hepatic ducts (Fig. 64-6E). The excised cyst should be examined grossly for malignancy, and then the specimen should be sent for frozen section. If malignancy is present at the surgical margins, the resection may be extended either proximally or distally with the possibility of a pancreaticoduodenectomy to obtain negative margin and adequate lymph node dissection.
FIGURE 64-6 Type I choledochal cyst resection and biliary reconstruction with Roux-en-Y hepaticojejunostomy. A. Exposure of cyst and gallbladder. B. Cholecystectomy and anterior dissection of the distal choledochal cyst. C. Distal extent of the cyst identified, encircled, and opened. D. Posterior dissection proceeds caudad to cephalad. E. Dissection proceeds until normal hepatic duct is identified. F. Cyst is transected and removed at normal duct. G. Excision is complete; reconstruction proceeds with a Roux-en-Y hepaticojejunostomy. If the bifurcation is involved, right and left hepaticojejunostomies can be performed. H. One-layer hepaticojejunostomy
Reconstruction of the biliary tree is typically performed with a Roux-en-Y hepaticojejunostomy at the bifurcation with a single anastomosis or multiple individual anastomoses with each of the hepatic ducts (Fig. 64-6F). A suitable segment of intestine is mobilized with a Roux-en-Y jejunal limb, approximately 60 cm in length, and the anastomosis is created with a standard retrocolic end-to-side Roux-en-Y hepaticojejunostomy, using a single layer of absorbable suture (Fig. 64-6G,H).

**Type II Cysts.** The recommended procedure for type II choledochal cysts is complete cyst excision. After the cyst has been exposed, the common bile duct wall defect should be closed transversely with or without a T-tube. A transverse closure helps minimize potential narrowing or stricturing of the common bile duct. These patients should also undergo a cholecystectomy at the time of cyst excision. Recently, resection of type II cysts has been completed successfully via a laparoscopic approach.

**Type III Cysts.** Because these cysts are unusual and have an overall lower rate of malignant transformation, reports of surgical excision of choledochoceles are uncommon. Primary management of choledochoceles is by ERCP with endoscopic unroofing of the choledochocele and sphincterotomy of the common bile duct.9,41 Surgical management is much less common in patients with choledochoceles compared to patients with other choledochal cysts. Although uncommon, surgical intervention for choledochoceles is needed for patients in whom sphincterotomy is very difficult or there is concern for malignancy.

The surgical approach for choledochoceles involves complete excision of the cyst and is approached via transverse duodenotomy in the second or third portion of the duodenum. Prior to duodenotomy, cholecystectomy is performed and then the ampulla can be localized by passing a biliary Fogarty catheter into the duodenum via the transected cystic duct. The anatomy can also be better defined via extensive Kocher maneuver and intraoperative ultrasound. The common bile duct and pancreatic duct must be identified to prevent injury to the pancreatic duct. After the duodenotomy, the pancreatic duct should be intubated with a small silastic tube so that the intraduodenal biliary cyst can be excised. The cyst is excised and a sphincterotomy can be
done by suturing the duodenal mucosa to the bile duct mucosa and pancreatic duct mucosa individually using interrupted absorbable sutures. A piece of 5- or 8-Fr plastic tubing can be placed into the pancreatic duct and secured with a single absorbable suture as a temporary stent to prevent acute pancreatitis. Finally, the duodenotomy is closed in a transverse fashion. It is highly unlikely that a Whipple procedure is required and should be considered only if malignancy is suspected.

**Type IV Cysts.** Type IVA and IVB cysts are managed similarly to type I cysts with regard to cholecystectomy, extrahepatic cyst excision, and biliary enteric anastomosis. However, the procedures are technically more challenging, and complete removal is not always possible for type IV cysts because of multiple extrahepatic cysts and intrahepatic cysts. Furthermore, these patients will most likely need reconstruction proximal to the bifurcation that involves anastomosing individual hepatic ducts. If 1 lobe of the liver is predominantly involving the intrahepatic cyst, then hepatic lobectomy should be recommended. In many situations, bilobar cyst disease remains, leaving this area at risk for malignancy. The long-term management in this situation is controversial. Intrahepatic disease in type IVA cysts and Caroli disease are prone to secondary biliary cirrhosis, hepatic atrophy, and portal hypertension. If the liver parenchyma is not cirrhotic and there is no evidence of intrahepatic duct malignancy, then the hepatic parenchyma should be preserved, even in the setting of stones or strictures. If cirrhosis is unilateral or segmental, resection of the involved parenchyma is necessary. Transhepatic biliary stents may be especially helpful for managing patients with type IV cysts, particularly those with type IVA cysts that extend into the intrahepatic ducts. The stents allow for proper decompression, alleviating chronic inflammation; may prevent or facilitate the management of long-term complications, such as biliary stasis, stones, cholangitis, and cirrhosis; and may be used for surveillance for malignant transformation.

Oncologic principles should be followed in cases in which malignancy is involved. If no metastatic disease is present and the vascular supply to the uninvolved hepatic parenchyma can be preserved, then resection of the involved bile ducts and adjacent parenchyma and lymph node dissection are indicated. In rare cases, extensive resections involving combined hepatic and pancreatic resection may be necessary. In cases in which metastatic disease is present, palliative stenting of the bile ducts is indicated.
**Type V Cysts.** Type V choledochal cyst (Caroli disease) is a difficult condition to manage, and the specific recommendations are not well defined. Current recommendations are to begin with conservative management treating infectious complications with drainage, stone extraction, antibiotics, and ursodiol. Although Caroli disease may be diffuse and bilobar, it is often confined to a single lobe and typically on the left side. Similar to type IVA cysts, Caroli disease, if unilateral or with segmental involvement with cirrhosis, can be managed by resection of the involved parenchyma, resulting in decreased incidence of recurrent cholangitis, pancreatitis, and cholestasis and decreased need for invasive procedures. Bilobar Caroli disease is a challenging problem. The use of ursodiol and antibiotics may improve bile flow and reduce the incidence of biliary stones, sludge, and cholangitis. In the absence of cirrhosis or malignancy, Roux-en-Y hepaticojejunostomy with bilateral transhepatic silastic stents may be indicated to improve biliary drainage. Following operative management, the stents are left in place for 6 to 12 months, depending on the extent of intrahepatic stones and strictures. Patients who continue to have recurrent cholangitis or recurrent stones often require indefinite transhepatic stenting. Patients with Caroli disease and progressive liver disease and cirrhosis should be considered for liver transplantation. The timing for when transplantation should be pursued is still under debate. Since patients with Caroli disease may also have polycystic kidney disease, combined liver-kidney transplants have had excellent outcomes. Mabrut and colleagues performed a multicenter study that included 155 patients with type V choledochal cysts from Western surgical centers. Patients underwent either hepatic resection (75%) or liver transplantation (19%) with excellent or good results achieved in 86% of patients. Five-year overall survival was 97% after liver resection and 89% after liver transplant.

**OPERATIVE RESULTS**

Early postoperative complications include pancreatitis, anastomotic leakage, cholangitis, and wound infection. Most series show morbidity rates of 9% to 41% and mortality rates of 0% to 3.3%.

The median length of stay ranges from 7 to 12 days after surgery; patients who undergo a laparoscopic approach have a slightly decreased hospital stay but longer operative time. Late postoperative complications include the formation of intrahepatic...
strictures and stones, anastomotic stricture, malignancy, cirrhosis, and intrahepatic abscess formation.

However, long-term results following resection of a benign choledochal cyst with biliary reconstruction are generally excellent, especially with type I cysts. The rate of biliary stricture had been found be very low. The management of more proximal cysts can be more challenging, particularly in the presence of extensive intrahepatic stone disease and liver damage. Type IVA cyst patients have the greatest risk for intrahepatic calculi and stricture formation secondary to the intrahepatic cystic disease. A series by Cho and associates examinated 204 patients with a mean follow-up of 14 years. Patients with type IVA disease with dilated intrahepatic ducts developed strictures at a rate of 24%, with virtually all presenting with cholangitis. In contrast, management with large-bore silastic transhepatic stenting results in 90% success without recurrent cholangitis. Patients remain at long-term risk for cholangitis, postoperative biliary strictures, intrahepatic stones, pancreatitis, or malignancy.

Summary

Choledochal cyst disease is uncommon. The presentation of the disease is more common in children but has been increasing in the adult population, especially in Western countries. Currently, the diagnosis in adults is based on cross-sectional imaging and cholangiography, primarily CT and MRCP. The consequences of not treating choledochal cyst disease can lead to malignant degeneration. The majority of cases of biliary cysts can be treated effectively with cholecystectomy, cyst excision, and biliary-enteric reconstruction. Long-term follow-up is necessary for surveillance of cancer, cholangitis, intrahepatic stones, and postoperative biliary strictures.

BENIGN BILIARY STRICTURES

Benign biliary strictures include several diverse clinical entities that share the common characteristic of biliary obstruction. Although advances in medical technology have greatly improved their management, bile duct strictures continue to pose a significant clinical challenge. Many of these strictures result from iatrogenic injuries, often in young patients who are otherwise in
good health and expected to live for years. Improper management may result in life-threatening complications including cholangitis, portal hypertension, biliary cirrhosis, and end-stage liver disease. Proper diagnosis and treatment are essential in preventing these complications.

Benign biliary strictures may affect the intrahepatic or extrahepatic bile ducts or both, and may be solitary or multiple. There are numerous etiologies of benign bile duct strictures (Table 64-2). The vast majority of strictures occur following injury to the bile duct during cholecystectomy; however, other procedures in the upper abdomen may injure the biliary tract, especially procedures involving the liver, pancreas, and stomach/duodenum. Inflammatory conditions such as pancreatitis, gallstone disease, and primary sclerosing cholangitis (PSC) are also important causes of benign bile duct strictures.

### TABLE 64-2: ETIOLOGY OF BENIGN BILIARY STRICTURES
Congenital

Biliary atresia

Postoperative Strictures

Laparoscopic cholecystectomy
Open cholecystectomy
Common bile duct exploration
Injury at other operative procedures
  Gastrectomy
  Hepatic resection
  Portacaval shunt
  Biliary-enteric anastomotic stricture
  Pancreatic surgery
  Liver transplantation
Blunt or penetrating trauma
Endoscopic or percutaneous biliary intubation

Strictures Due to Inflammatory and Other Conditions

Primary sclerosing cholangitis
Chronic pancreatitis
Cholelithiasis and choledocholithiasis
Cholangiohepatitis and other parasitic disease
Sphincter of Oddi stenosis
Duodenal ulcer
Granulomatous lymphadenitis
Secondary sclerosing cholangitis
  Toxic drugs
  Infectious cholangiopathy from AIDS
  Hepatic allograft rejection
  Graft-versus-host disease in bone marrow transplantation
  Histiocytosis X
  Congenital biliary abnormality
  Mast cell cholangiopathy

Postoperative Biliary Stricture
The introduction and widespread use of laparoscopic cholecystectomy in the 1990s resulted in a significant increase in the frequency of biliary injuries and associated bile duct strictures. Postoperative bile duct injuries may present early in the postoperative period with biliary leak or months to years later with jaundice or cholangitis from biliary stricture. Proper management begins with delineation of biliary anatomy followed by repair. Nonoperative balloon dilatation via percutaneous transhepatic or endoscopic routes is appropriate in select patients with intact biliary-enteric continuity. Operative repair, however, remains the mainstay of treatment in patients with benign strictures.

**INCIDENCE**

Most bile duct injuries and strictures occur in patients following abdominal surgery in the right upper quadrant. Cholecystectomy is performed on over 750,000 patients on an annual basis in the United States and accounts for over 90% of postoperative biliary strictures and injuries. Although the exact incidence of injuries is unknown because many cases go unreported, numerous studies have attempted to define the incidence and mechanisms of bile duct injuries associated with cholecystectomy. An incidence of 1 to 3 major bile duct injuries per 1000 cases was consistently reported during the era of open cholecystectomy. Roslyn and colleagues\(^4\) demonstrated a 0.2% incidence of major bile duct injuries from a series of over 42,000 open cholecystectomies. A literature review by Strasberg and associates\(^5\) of over 25,000 open cholecystectomies performed since 1980 revealed a 0.3% incidence of major bile duct injuries. In the 1990s, Strasberg and associates\(^5\) reviewed nearly 125,000 laparoscopic cholecystectomies and reported an overall incidence of biliary injuries of 0.85% and an incidence of major injuries of 0.52%. Recently, multiple large studies from numerous centers have estimated the rate of major bile duct injury with laparoscopic cholecystectomy to be 0.08% to 0.6%.\(^6\)-\(^8\) A recent 5-year review of the New York State Planning and Research Cooperative System (SPARCS) showed that over 156,000 patients had undergone laparoscopic cholecystectomy and only 149 biliary injuries were identified, indicating a rate of 0.08%.\(^6\) Therefore, it appears that the incidence of bile duct injury associated with laparoscopic cholecystectomy is now comparable to that with open cholecystectomy. This improvement likely reflects increased experience, improved instrumentation, and movement beyond the “learning
curve.” Finally, the effect of new techniques such as single-port laparoscopic cholecystectomy or the value of robotic technology in the safe performance of laparoscopic cholecystectomy is yet to be determined. However, some concern has been expressed related to the learning curve of such procedures when compared with the established laparoscopic procedure.

In the early 1990s, many authors ascribed the increased incidence of bile duct injuries with laparoscopic cholecystectomy as a “learning curve” associated with the new technique and projected that the rate of injury associated with laparoscopic cholecystectomy would decline with time. The rate of bile duct injuries appears now to have stabilized or perhaps decreased in the laparoscopic era; however, with newer graduates having less experience with open cholecystectomy, the rate of bile duct injury associated with a difficult cholecystectomy may be on the rise for the open procedure. Similarly, due to their lack of experience, conversion from laparoscopic cholecystectomy to open cholecystectomy may increase the rate of bile duct injuries. An “extreme” vasculobiliary injury with injury to the hepatic artery and/or portal vein may occur in conversion from laparoscopic to open cholecystectomy in the presence of severe inflammation in and around the gallbladder when a fundus-down cholecystectomy is performed. Severe hemorrhage is common and is caused by dissection behind the cystic plate into the right portal pedicle involving vascular injury to a major hepatic artery and a portal vein. This “extreme” vasculobiliary injury can lead to infarction of the liver or diffuse bile duct infarction requiring possible hepatectomy or need for urgent liver transplantation or leading to death.

PATHOGENESIS

Several factors are associated with increased risk of bile duct injuries at the time of cholecystectomy. Some of these factors may be pathologic, anatomic variations, and/or technical problems that differ in the open or laparoscopic approach. Ultimately, the final common pathway of most injuries is either a technical error or misinterpretation of the anatomy. The chapter will focus primarily on laparoscopic cholecystectomies because 98% of cholecystectomies are initially started as a laparoscopic procedure. The “classic” biliary injury during laparoscopic cholecystectomy includes misidentification by the surgeon of the common bile duct as the cystic duct or misidentification of an aberrant right sectoral duct as the cystic duct (Fig. 64-
FIGURE 64-7 Classic laparoscopic bile duct injury. Confusion of the common bile duct with the cystic duct leads to clipping and division of the common bile duct. In many cases, the common hepatic duct will not be clipped but will instead be divided by scissors or cautery. (Reproduced with permission from Davidoff AM, Pappas TN, Murray EA, et al: Mechanisms of major biliary injury during laparoscopic cholecystectomy, Ann Surg 1992;Mar;215(3):196-202.)

Pathologic Factors. A number of patient-related factors have been associated with bile duct injury. Patients with acute cholecystitis may have severe inflammation in the porta hepatis and the Calot triangle, which can make an operation difficult. Patients also with complicated gallstone disease have a higher risk of injury than patients with chronic cholecystitis, symptomatic cholecystitis, or biliary colic. Tang and Cuschieri reported that
complex cases, which included patients with acute cholecystitis, cholangitis, and gallstone pancreatitis, are associated with an increased incidence of bile duct injuries (1.2% vs 0.4%) versus other indications for laparoscopic cholecystectomy. These patients also have a higher rate of conversion to open cholecystectomy (30% vs 3%).

**Anatomic Variations.** Anatomic variations can also contribute to bile duct injury. A congenitally short cystic duct or a duct that appears shortened by an impacted stone may also lead to misidentification of the common bile duct, resulting in injury or transection. Other high-risk congenital anatomic anomalies include a long common wall between the cystic and common bile duct or the cystic duct inserting into the right hepatic duct. The cystic duct has a very variable pattern ranging from joining the common hepatic duct quite high, almost at the biliary confluence, to running parallel to the common hepatic duct before inserting into the common bile duct almost at the level of the pancreas. The risk of bile duct injury also appears to be increased in patients with obesity, chronic inflammation, excessive fat in the dissection area, inadequate exposure, poor or excessive clip placement, injudicious use of electrocautery, and bleeding into the operative field.

**Technical Factors.** Several technical factors associated with laparoscopic cholecystectomy make it prone to bile duct injury. First, standard laparoscopy gives a limited perspective from its end, viewing a 2-dimensional picture of the operative field. The classic laparoscopic injury occurs when the cystic duct and the common bile duct are aligned in the same plane, leading to clipping and dividing the common bile duct. Retraction of the gallbladder infundibulum excessively cephalad aligns the cystic and common bile duct, leading to misidentification and injury. As the operative dissection is carried cephalad, the common hepatic duct may also be transected, often without recognition, resulting in a postoperative bile leak. The right hepatic artery may also be injured, creating excessive bleeding. This classic injury is estimated to occur in over 75% of major bile duct injuries referred to major centers. The classic laparoscopic injury is usually also associated with excision of a segment of bile duct, making the proximal extent of the injury high, usually at or near the hepatic duct bifurcation.

There is also a growing understanding of surgeon cognitive factors associated with bile duct injury during laparoscopic cholecystectomy. A
report examined 252 laparoscopic cholecystectomy bile duct injuries using the human error factor and cognitive science techniques and found that 97% of injuries were due to a visual perceptual illusion or inadequate visualization.\textsuperscript{53} In a subsequent study from the same group, one of the main explanations for the surgeon’s frequent inability to recognize a bile duct injury associated with laparoscopic cholecystectomy appears to be confirmation bias, which is the propensity to seek clues to confirm a belief and to discount clues that might discount that belief.\textsuperscript{54} While cognitive factors are important for understanding the psychological issues associated with bile duct injuries, surgeons must continue to have appropriate corrective mechanisms in place to minimize the chance of these injuries, including knowledge of anatomy, typical mechanisms of injury, appropriate level of suspicion, and logic.\textsuperscript{55}

The role of intraoperative cholangiography in preventing bile duct injury remains controversial, with mixed results from reported series. A large series in Australia demonstrated a protective effect,\textsuperscript{56} whereas a review from the Veteran’s Administration Hospitals demonstrated that bile duct injury occurred more commonly in patients undergoing cholangiography (0.7% vs 0.2%).\textsuperscript{45} Clinical information from patients in the Texas Medicare claims data from 2000 through 2009 was examined, and the rate of injury was found to be higher when intraoperative cholangiography was not used.\textsuperscript{57} In this study, surgeons who routinely performed intraoperative cholangiography had a lower rate of injuries than those who did not; however, when confounders were controlled with instrumental variable analysis, there was no statistically significant association between intraoperative cholangiography and common duct injury. This led to the conclusion that intraoperative cholangiography is not effective as a preventive strategy against common duct injury during cholecystectomy. Whether or not intraoperative cholangiography actually prevents bile duct injury, the procedure can often lead to early recognition of the injury and, therefore, potentially minimize the injury and its associated morbidity (Fig. 64-8).
FIGURE 64-8  Intraoperative cholangiogram obtained during laparoscopic cholecystectomy. Cholangiogram demonstrates an injury to the common bile duct (which is clipped such that contrast does not fill the proximal biliary tree). Contrast fills the normal distal bile duct and duodenum.

The use of fluorescent cholangiography has recently been introduced to help determine biliary anatomy. Studies show that the frequency of detection of structures ranged from 72% to 100% for the cystic duct, 33% to 100% for the common hepatic duct, 50% to 100% for the common bile duct, and 25% to 100% for the common duct–common hepatic duct junction. The best technical approach in preventing and limiting bile duct injuries, regardless of
the use of cholangiography, includes methodical dissection with careful exposure and identification of the structures of the triangle of Calot. The operative technique for laparoscopic cholecystectomy that defines the “critical view of safety” is a corrective mechanism that helps prevent misidentification and injury of the major bile ducts. In this method, the triangle of Calot is cleared of fat and fibrous tissue. Only 2 structures are connected to the lower end of the gallbladder once this is done, the cystic duct and cystic artery, and the lowest part of the gallbladder attachment to the liver is exposed. Once the critical view is attained, the cystic duct and artery may be clipped and divided, as they have been conclusively identified. Failure to achieve the critical view is an indication for conversion or possible cholangiography. There are studies containing several thousand patients in which the critical view of safety was used for target identification without a biliary injury due to misidentification. The critical view of safety is part of the Culture of Safety in Cholecystectomy (COSIC), and this problem has been addressed by the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) in a novel effort called “Safe Cholecystectomy.”

Physiologic Factors. Several physiologic processes have been implicated in the formation of bile duct strictures. Ischemia of the bile duct from excessive periductal dissection may have an important role in the formation of postoperative anastomotic strictures. Studies show that the blood supply to the ducts can be thought of having 3 elements: afferent arteries, marginal arteries, and the epicholedochal plexus. The afferent arteries are branches of the hepatic arteries or less commonly of the superior mesenteric artery or other upper abdominal arteries. The marginal arteries lie on and run parallel to the long axis of the bile ducts. Anatomically, these are the major arteries of the common bile duct located at the 3 and 9 o’clock positions that can be injured or divided by unnecessary dissection during cholecystectomy, or more commonly, the bile duct can be excessively “skeletonized” while performing a bile duct anastomosis.

Fibrosis and scarring can be intense following a bile duct injury. In canine models, bile duct ligation results in an elevation of bile duct pressure that is immediate and sustained and is accompanied by an increased bile duct diameter and formation of high local concentrations of bile salts at the canalicular membrane. A month following bile duct ligation, the bile duct wall is thickened, will have reduced mucosal folds, and will have loss of
surface microvilli with epithelial degeneration. On pathologic staining 2 weeks after ligation, there is evidence of increased synthesis of collagen and proline hydroxylase activation. An animal model of bile duct injury demonstrated healing in traumatized bile duct tissue to occur in a mode of overhealing, implicating myofibroblasts as the main cause of contracture of scar and stricture of the bile duct.\textsuperscript{64} Inflammation in the surrounding tissues compounds the problem by encouraging fibrosis, especially when associated with bile leakage.

Injuries and strictures of bile ducts occur less commonly in association with other operative procedures. After cholecystectomy, common bile duct exploration is the next most frequently associated procedure with stricture, typically occurring at the site of choledochotomy or an impacted stone. Procedures requiring biliary-enteric anastomoses may be complicated by postoperative stricture. Typically, these procedures involve choledochoenteric or hepaticoenteric Anastomosis in such cases as reconstruction after pancreaticoduodenectomy, bile duct resection for mid-bile duct tumors, and excision of choledochal cysts. Gastrectomy and hepatic resection are the most common nonbiliary operations associated with postoperative strictures. Injuries associated with gastrectomy typically occur during pyloric and proximal duodenal dissection associated with closure of the duodenal stump or with creating a Billroth I gastroduodenostomy. Injuries during hepatic resection often take place during dissection of the hepatic hilum. Bile duct injury and stricture are also associated with hepatic transplantation, pancreatic procedures, and penetrating or blunt trauma. Finally, the recurrence of stricture after an initial attempt at repair is not uncommon and may occur over a decade following initial repair (Fig. 64-9).\textsuperscript{65}
FIGURE 64-9 The cumulative percentage of recurrent strictures is shown with respect to the time interval from the initial repair to the next repair. (Adapted with permission from Pitt HA, Miyamoto T, Parapatis SK, et al: Factors influencing outcome in patients with postoperative biliary strictures, *Am J Surg* 1982;July;144(1):14–21.)

CLASSIFICATION

Strictures and injuries to the bile duct vary widely in their complexity and nature. The ease of management, operative risk, and outcome of biliary injuries vary considerably depending on the location and the type of injury. Injuries associated with laparoscopic cholecystectomy are often complex, located at or near the level of the hepatic duct bifurcation, and potentially include 1 or more hepatic duct branches. Minor injuries to the bile duct include lacerations of the bile duct, clip placement on an intact bile duct, injury via electrocautery, or avulsion of the cystic duct.

A number of classification systems of major bile duct strictures have been presented, with the traditional classification being that described by Bismuth (Fig. 64-10), which classifies major injuries based on the level of obstruction of the biliary tree with respect to the hepatic duct confluence or the involvement of an aberrant right sectoral hepatic duct with or without a concomitant hepatic duct stricture. A drawback of the Bismuth classification system is that patients with limited strictures, isolated right
hepatic duct strictures, or cystic duct leaks cannot be classified. The Strasberg classification system has been developed to classify all types of injury and is used extensively in describing bile duct injuries associated with laparoscopic cholecystectomy (Table 64-3).\textsuperscript{60}

\textbf{FIGURE 64-10} Bismuth classification system. Classification of bile duct strictures based on the level of the stricture in relation to the confluence of the hepatic ducts. Types III, IV, and V are usually considered complex injuries. (Reproduced with permission from Blumgart LH: The Biliary Tract. Clinical Surgery International Series, Vol. 5. Edinburgh, Scotland: Churchill Livingstone; 1983.)
TABLE 64-3: STRASBERG CLASSIFICATION OF BILIARY INJURY AND STRICTURE

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Injury to small ducts in continuity with the biliary system, with cystic duct leak</td>
</tr>
<tr>
<td>B</td>
<td>Injury to sectoral duct with consequent obstruction</td>
</tr>
<tr>
<td>C</td>
<td>Injury to sectoral duct with consequent bile leak</td>
</tr>
<tr>
<td>D</td>
<td>Lateral injury to extrahepatic ducts</td>
</tr>
<tr>
<td>E₁</td>
<td>Stricture &gt;2 cm distal to bifurcation</td>
</tr>
<tr>
<td>E₂</td>
<td>Stricture &lt;2 cm distal to bifurcation</td>
</tr>
<tr>
<td>E₃</td>
<td>Stricture at bifurcation</td>
</tr>
<tr>
<td>E₄</td>
<td>Stricture involving right and left bile ducts; ducts are not in continuity</td>
</tr>
<tr>
<td>E₅</td>
<td>Complete occlusion of all bile ducts</td>
</tr>
</tbody>
</table>

PRESENTATION

Most patients with bile duct injuries unfortunately are not recognized at the time of laparoscopic cholecystectomy. After open cholecystectomy, only 10% of injuries are suspected after the first week, but nearly 70% are diagnosed within the first 6 months after operation. However, injuries after laparoscopic cholecystectomy are recognized earlier more likely because of heightened awareness and suspicion.

Large series reviews have demonstrated that less than one-third of major bile duct injuries are detected at the time of injury during laparoscopic cholecystectomy. Possible indications that a bile duct injury occurred intraoperatively include a persistent and unexpected bile leak, atypical anatomy, or a second bile duct discovered during dissection. Injuries may also be discovered if the removed gallbladder specimen and cystic duct are carefully examined to ensure normal duct anatomy. Intraoperative cholangiography will also diagnose bile duct injuries at the time of cholecystectomy and may minimize injury, allowing early repair (see Fig. 64-8).

The clinical presentation of patients with a bile duct injury in the early postoperative period depends on the type of injury. In most cases, the injury is associated with uncontrolled bile leakage into the peritoneal cavity, while
in others, the duct is completely ligated by clip placement, leading to obstructive jaundice usually without cholangitis. Patients with significant bile leaks generally present within the first week after operation with abdominal pain, distention, nausea, vomiting coupled with fever, or other signs of sepsis. Prompt investigation is required if patients have bilious drainage from incision sites or from intraoperatively placed drains. Bile leaks result in biliary ascites with associated chemical peritonitis if allowed to drain freely into the abdominal cavity, or alternatively, bile can become loculated, resulting in biloma (Fig. 64-11) or, if infected, a subhepatic or subdiaphragmatic abscess. In the latter scenario, presentation is more subtle with low-grade fever and localized abdominal pain. Since significant abdominal complaints are uncommon after uncomplicated laparoscopic cholecystectomy, all patients with such symptoms should be appropriately evaluated without delay for possible bile leak to prevent progression to frank sepsis. Failure to recognize a major bile leak or to institute appropriate treatment can result in life-threatening sepsis and the development of multisystem organ failure. In the landmark series of 200 major bile duct injuries treated at the Johns Hopkins Hospital, 3 patients were transferred to a tertiary care center and died of complications of sepsis secondary to delayed or inadequate treatment.
Bile duct strictures may also present months to years after the original operation. Patients with a slowly evolving stricture may have nonspecific abdominal complaints, jaundice, pruritus, cholangitis, or derangements in liver function tests. In addition, patients with an isolated right sectoral hepatic duct injury may present with a history of unexplained fevers, pain, or generalized malaise. Episodes of cholangitis are typically mild and respond effectively to antibiotics. Less often, patients can present with painless jaundice, which can be confused with a malignant stricture.

The findings on physical examination are usually not specific. Abdominal distention and pain may be seen in patients with bile peritonitis or focal tenderness if the patient presents with a collection or abscess. If the patient has jaundice, there may be multiple excoriations from pruritus. Hepatomegaly may be present in patients with chronic biliary obstruction or possible splenomegaly if there is any portal hypertension from portal venous injury or severe underlying hepatocellular damage.

**DIAGNOSIS**

Patients presenting with a biliary leak from injury usually present without evidence of biliary obstruction, and bilirubin levels are normal or slightly elevated due to absorption of bile from the peritoneal cavity. Patients with postoperative bile leak or cholangitis will also have an elevated white blood cell count, pyrexia, or occasionally frank sepsis. Patients with postoperative bile duct strictures typically reveal a stereotypical biochemical profile of cholestasis. In particular, liver function tests typically consist of an elevated alkaline phosphatase and normal or slightly elevated liver transaminases (alanine and aspartate aminotransferases). Serum bilirubin levels are usually elevated in the range of 2 to 6 mg/dL. In rare cases, patients with long-term obstruction will present late in the course of disease with cirrhosis, diminished serum albumin, and abnormal coagulation studies from altered hepatic synthetic function.

Definitive diagnosis for bile duct strictures and injuries requires radiographic imaging. Ultrasound and abdominal CT scan are both helpful in
patients who present in the early postoperative period for the detection of bilomas and biliary ascites, as well as bile duct dilatation from obstruction. Ultrasound has little value in assessing the extent of a stricture and is unhelpful if the biliary tree is decompressed. Abdominal CT scan is usually the best first-line study often showing a dilated biliary tree or intra-abdominal collections or ascites, which can direct further investigations. The CT should be performed with arterial-phase contrast to evaluate for concomitant vascular injury. Nuclear medicine imaging with technetium-hepatobiliary iminodiacetic acid (HIDA) scanning can demonstrate bile leakage noninvasively but typically does not have the sensitivity to define the specific anatomic site of injury. MRCP has been demonstrated to be an effective noninvasive method for demonstrating biliary leakage or obstruction, as well as precisely defining biliary anatomy and the nature of the injury, such that in selected cases, this technique may be all that is needed to define anatomy prior to definitive repair (Fig. 64-12). Lastly, sinography, typically performed by injecting water-soluble contrast via operatively placed drains, can define the biliary anatomy and the source of bile leakage.
FIGURE 64-12 Diagnostic MRCP demonstrating biliary anatomy associated with a cystic duct leak after laparoscopic cholecystectomy. There is an intact biliary system with extravasation of contrast in the subhepatic space.

Cholangiography currently remains the gold standard for evaluating the biliary tree. Endoscopic retrograde cholangiography (ERC) is performed via a distal approach to the biliary tree and is useful only in patients if the native bile duct is intact, such as with partial injuries or after end-to-end repair. ERC is the procedure of choice for patients suspected of cystic duct leaks (Fig. 64-13A) or leaks from peripheral hepatic radicals (ducts of Lushka). In these cases, the biliary leak may be effectively controlled with the use of an
endoprosthesis. Most cases of major bile duct injury, however, are associated with complete duct transection, and the cholangiogram via the retrograde endoscopic route will demonstrate a normal distal bile duct terminating in misapplied clip (Fig. 64-13B). Therefore, ERC will not define the site of bile leakage nor the proximal anatomy necessary for reconstruction. In such cases, PTC is usually necessary to define the proximal biliary anatomy and the site of injury (Fig. 64-14). In addition to delineating the anatomy, a percutaneous biliary drainage catheter should be placed at the time of PTC to decompress the biliary tree, treat cholangitis, and control the biliary leak. Percutaneous biliary drainage catheters will also be useful at the time of operative repair as a guide for dissection and identification of the transected bile duct, which is often retracted high into the liver hilum. Finally, in cases in which biliary-enteric continuity exists, percutaneous catheters allow access for balloon dilatation.
**FIGURE 64-13**  
A. Endoscopic retrograde cholangiopancreatogram demonstrating cystic duct leak.  
B. Endoscopic retrograde cholangiopancreatogram with multiple clips across the common bile duct without visualization of the proximal biliary tree in a patient with total transection of the common bile duct during laparoscopic cholecystectomy.

**FIGURE 64-14**  
Percutaneous transhepatic cholangiogram in a patient with complete transection of the common hepatic bile duct. Note the surgical clips near the cutoff point.
Significant arterial injury associated with major bile duct injury has been increasingly reported in recent years. The “classic” biliary injury during laparoscopic cholecystectomy in which the common bile duct is mistaken for the cystic duct often includes injury to the right hepatic artery as it enters either above or below the hepatic duct. While this injury may cause bleeding at the time of operation, the arterial injury often is unnoticed, usually resulting in arterial occlusion or less commonly a hepatic artery pseudoaneurysm. In a large study by Stewart et al\textsuperscript{71} on combined right hepatic artery and bile duct injury, there were 7 pseudoaneurysms compared to 77 right hepatic artery occlusions. The incidence of disruption of the right branch of the hepatic artery during major bile duct injury ranges between 12\% and 39\%.\textsuperscript{72} However, the presence of an arterial injury does not appear to affect either early or late outcomes.\textsuperscript{71,73} Due to the recognized association of vascular injuries during laparoscopic bile duct injuries, especially if there is a history of excessive bleeding at the time of cholecystectomy, a CT scan with arterial and venous phase contrast or arteriography should be obtained. Some authors believe that if arterial injury has occurred, biliary reconstruction should be delayed to decrease the risk of late stricture recurrence.\textsuperscript{60} In patients presenting in a delayed manner after cholecystectomy, the combination of biliary and vascular injuries often leads to segmental or lobar atrophy, which may suggest a role for hepatic resection rather than reconstruction.

**PREOPERATIVE MANAGEMENT**

The timing of presentation is often a primary determinant of the preoperative management of a patient with a postoperative bile duct stricture or injury. In the early postoperative period, patients with a bile leak associated with a bile duct injury are often either septic due to intra-abdominal infections or otherwise manifesting a systemic inflammatory response from chemical peritonitis associated with the bile leak. Treatment and control of sepsis may require broad-spectrum parenteral antibiotics, percutaneous biliary drainage, and percutaneous or, rarely, operative drainage of bilomas. Once sepsis is controlled, there is no hurry in proceeding with surgical reconstruction of the bile duct injury. Most biliary fistulae can be controlled with the combination of proximal biliary decompression and external drainage. After early control and clinical improvement, the patient may be discharged home for several
weeks to permit return of overall health and for the resolution of inflammation in the periportal region. Finally, as experience has been gained, selected patients, such as those with the bile duct clipped yet without a bile leak, may be managed without preoperative biliary catheters, if favorable anatomy is delineated by MRCP.

It should be stressed that despite the belief of many surgeons that a suspected bile leak warrants urgent reoperation, exploration with an attempt at repair should be avoided early after presentation with a bile leak. In this situation, exploration often reveals marked inflammation associated with bile spillage and small, decompressed bile ducts retracted high into the porta hepatis, making recognition of the injury and repair virtually impossible. Instead of proceeding to urgent exploration, a more prudent approach is to define biliary anatomy via preoperative cholangiography and to control the bile leak with percutaneous stents. Early operative intervention to deal with bile collections or ascites is not usually required because the intraperitoneal bile either can be drained percutaneously or is simply absorbed by the peritoneal cavity. Delayed reconstruction, with facilitation by percutaneous biliary catheters, allows for the most favorable operative results, especially when concurrent hepatic artery injury is suspected.

Patients who present with a biliary stricture remote from the initial operation usually experience symptoms of cholangitis that necessitate urgent cholangiography and biliary decompression. The choice of technique depends on the nature of any prior repair. If the native bile duct is intact, endoscopic drainage with stent placement can sometimes be achieved. If a prior hepaticojejunostomy has been performed, transhepatic biliary drainage will be necessary for diagnosis. Both parenteral antibiotics and biliary drainage are central to controlling sepsis. Patients who present with jaundice without cholangitis should undergo either ERC or PTC to define the anatomy. As with patients presenting early in the postoperative period, ERC may not completely define the proximal biliary anatomy, making PTC the more favorable procedure. Preoperative biliary decompression in patients presenting with jaundice without cholangitis has not been demonstrated to improve outcome.

**OPERATIVE MANAGEMENT**

Operative repair for postoperative bile duct strictures is aimed at
reestablishing a reliable, long-term conduit for bile flow from the biliary tree to the gastrointestinal tract. Complications of an unsuccessful operative procedure include bile leak resulting in fluid collection or abscess, recurrent stricture with stones or sludge and potentially cholangitis, and biliary cirrhosis. To this end, the ideal technical procedure results in a tension-free, mucosa-to-mucosa repair to a segment of uninjured bile duct. Ideally, surgeons should also seek to maintain ductal length by not sacrificing tissue. Options for operative repair may include end-to-end repair, Roux-en-Y hepaticojejunostomy, or choledochoduodenostomy. The optimal operative procedure is contingent upon the timing of presentation, overall clinical status of the patient, level of injury, and type of injury.

**Injury Recognized at Initial Operation.** If injury to the bile duct is recognized at the time of initial cholecystectomy, the surgeon should consider his or her ability to technically perform immediate reconstruction and should consider seeking the counsel and assistance of a more experienced surgeon. Studies show that immediate open repair by an experienced surgeon is associated with reduced morbidity, shorter duration of illness, and lower cost. Each failed attempt at repair is associated with loss of bile duct length and exacerbation of a difficult situation. If the surgeon is unable to repair the injury and competent help is unavailable, no further attempt at dissection or removal of the gallbladder should be performed. Drains should be placed to control any bile leak and the patient referred immediately to a tertiary specialty center. If possible, the surgeon at the specialty center should be called from the operating room to guide decision making.

When the surgeon suspects an injury or variant anatomy, biliary anatomy must be clearly defined using intraoperative cholangiography and/or careful dissection, being cautious to avoid additional injury or devascularizing the bile duct. Conversion from laparoscopic to open cholecystectomy is often necessary to properly identify anatomy and the injury. Segmental or accessory duct injuries where the diameter of the bile duct is less than 3 mm and where the bile duct does not communicate with the major duct system or drain a large segment of hepatic parenchyma on cholangiography may be ligated. If bile ducts are 4 mm or larger in diameter or the cholangiogram shows sectoral or lobar drainage, then the ducts must be operatively repaired, as they likely drain multiple hepatic segments or an entire liver lobe.

Immediate intraoperative repair is indicated in most cases for a major
injury of the common hepatic or common bile duct. The nature of that repair is determined by the length of separation between opposed residual, viable ends of the injured duct. Partial common duct transections, involving less than 180-degree circumference of the biliary tree, may be closed primarily over a T-tube using interrupted absorbable sutures (Fig. 64-15). Transection of the common duct involving more than 180-degree circumference or complete transactions with an injury less than 1 cm in length can usually be repaired with an end-to-end anastomosis with a T-tube that exits either above or below the anastomosis via a separate choledochotomy. Primary reconstruction of the bile duct, however, should be used selectively and be avoided when the injury is near the bifurcation or when duct approximation cannot be accomplished without tension. A generous Kocher maneuver should be done to mobilize the duodenum out of the retroperitoneum and should be used to alleviate tension at the repair. In at least one series, a 100% restricture rate following primary end-to-end repair has been reported.\textsuperscript{74} Other series have shown better results and suggest the advantage that if a stricture occurs, endoscopic access for balloon dilation remains an option.\textsuperscript{75}
FIGURE 64-15 Primary end-to-end repair of the biliary tree over a T-tube. In general, this technique is used for partial transections of the bile duct, when there has been no associated loss of duct length. Note that the T-tube does not exit at the site of injury.

Transections of the bile duct high in the biliary tree or with significant loss of bile duct length cannot be repaired with a primary biliary anastomosis that remains tension-free. These injuries require reconstruction using a biliary-enteric anastomosis typically using Roux-en-Y hepaticojejunostomy to ensure a tension-free repair. In this situation, the distal bile duct should be oversewn, the injured tissue in the proximal end debrided, and then a biliary-enteric end-to-side anastomosis to the Roux-en-Y jejunal limb performed. Transhepatic silastic biliary stents should be placed to control potential
anastomotic leaks and for postoperative cholangiography. A peri-anastomotic drain should also be placed in all cases so that any potential postoperative leak is well controlled.

**Injury Recognized in the Immediate Postoperative Period.** Biliary injuries that are not appreciated in the intraoperative period may present in the first few days. The presentation may include bile drainage from the wound, bile peritonitis, or progressive jaundice. The initial management of a patient who presents in the delayed fashion following laparoscopic cholecystectomy depends on the nature of the injury and the mode and timing of presentation. Any elective repair should generally occur only after preoperative clinical optimization of the patient and after exact anatomy of the biliary system has been identified. Those presenting with biliary leak should have the bile leak and sepsis controlled prior to having definitive repair. In this situation, the result of reconstruction is almost always better if the definitive repair is made well after the leak and the consequent intra-abdominal inflammation and sepsis are controlled with percutaneous biliary drainage. Biliary spillage and marked inflammation can obscure fields and can make identification of ducts difficult, making urgent early laparotomy prior to biliary decompression problematic. Finally, the patient should be clinically stabilized prior to elective repair to correct fluid and electrolyte balances, anemia, and malnutrition. The repair is ideally performed 6 to 8 weeks after adequate control of the leak has been attained.

In patients who present with biliary stricture weeks to months after cholecystectomy, identification of the biliary system is also essential. In patients with a stricture and symptoms of cholangitis, the patient should be treated with broad-spectrum antibiotics until sepsis is controlled, followed by biliary decompression with transhepatic percutaneous catheter placement.

**Definitive Management of Bile Duct Stricture.** The goal of operative management of a bile duct stricture is the establishment of bile flow into the proximal gastrointestinal tract in a manner that prevents sludge, stone formation, cholangitis, restructure, and cirrhosis. The type of repair should be determined by several factors: previous history of attempted repair, location of stricture or injury, surgeon experience, and surgeon preference. Intraoperatively, biliary anatomy must be carefully defined followed by exposure of healthy proximal bile ducts. Care must be taken to avoid
excessive dissection and devascularization of tissue. A biliary-enteric anastomosis is performed using a mucosa-to-mucosa technique in a tension-free manner.

The preferred technique, with few exceptions, is a hepatico- or choledochojejunostomy to a Roux-en-Y limb of jejunum. End-to-end anastomosis after excision of the stricture or area of injury is not prudent due to the loss of bile duct length and associated fibrosis. Significant loss of bile duct length is also a strict contraindication to performing choledochoduodenostomy, which is unlikely to be performed in a tension-free fashion and is also associated with duodenal fistula if leak occurs.

The exact details of the reconstruction depend on the particular anatomic features of the stricture. For strictures where there is more than 2 cm of healthy common hepatic duct present (Bismuth I), a simple end-to-side biliary-enteric anastomosis will suffice. For strictures in which there is less than 2 cm of healthy common hepatic duct (Bismuth II) or the stricture involves the bifurcation of the hepatic duct but the left and right still communicate (Bismuth III), it may be necessary to lower the hilar plate and extend the dochotomy along a short length of the left hepatic duct to allow a common biliary-enteric anastomosis. Strictures that completely separate the right and left biliary system (Bismuth IV and V) require separate right and left biliary-enteric anastomosis. When duct length cannot be found outside of the hepatic parenchyma, an intraoperative ultrasound is essential to locate the segment II and segment III ducts. Often, a wedge of liver may need to be resected until an adequate duct can be found to do a biliary-enteric anastomosis.

The use of percutaneous biliary stents with elective reconstruction of the biliary tree remains a topic of debate for hepatobiliary surgeons. Preoperatively placed stents act as intraoperative aids for defining anatomy, especially if the stricture is located proximally. Stents left in place after reconstruction also allow postoperative cholangiography and control early anastomotic leaks in the immediate postoperative period. Many surgeons also advocate extended postoperative transanastomotic stenting, with the purpose of minimizing fibrosis and risk of late anastomotic stricture. In this setting, follow-up cholangiography will reveal early evidence of anastomotic stricture and provide access for balloon dilatation if necessary.

Biliary reconstruction with the technique of hepaticojejunostomy with a Roux-en-Y limb with transhepatic biliary stents is depicted in Figure 64-16.
Dissection of the porta hepatis is performed to clear any adhesions between the duodenum or colonic hepatic flexure to the gallbladder fossa, subhepatic space, or Glisson capsule. Preoperatively placed percutaneous stents are essential in assisting in dissection and bile duct identification in patients with a high bile duct transection. In patients with an intact but strictured bile duct, the duct is divided at the most distal portion of the stricture, and a segment of the strictured duct should be resected and sent to pathology for frozen section. The distal end of the stricture is then oversewn. The proximal extent of the duct should be debrided for a length not to exceed 5 mm to obtain healthy bile duct circumferentially for use in the anastomosis. Careful limited dissection is important to avoid vascular compromise to the bile duct.

Preoperatively placed percutaneous transhepatic catheters, which now protrude from the proximal end, are usually exchanged for soft silastic stents. Silastic stents range from 12 to 22 Fr in size, with multiple side holes that are generally interspersed along 40% of the length of the catheter. A radiologic guidewire is placed through the percutaneous transhepatic catheter; using the Seldinger technique, a series of progressively larger coudé catheters are passed over the guidewire in order to dilate the system for silastic stent placement. The silastic stent is arranged with the side holes extending beyond the anastomosis distally and within the liver parenchyma proximally. The end of the silastic stent without holes is brought through the hepatic parenchyma and out through the upper anterior abdominal wall. A Roux-en-Y jejunal limb is then created by mobilizing a suitable segment of intestine of approximately 60 cm in length. The anastomosis is then constructed with a standard end-to-side Roux-en-Y hepatico- or choledochojunostomy, typically using a single layer of 4-0 or 5-0 absorbable sutures.
FIGURE 64-16 Roux-en-Y hepaticojejunostomy reconstruction of biliary tree. A. Repair of common hepatic duct stricture with transhepatic ring catheter exiting at the bifurcation. The stricture has been resected, and the distal biliary tree is oversewn. The hepaticojejunal anastomosis can then be performed over the ring catheter, or the ring catheter can be exchanged for a silastic transhepatic stent. B. The silastic transhepatic stent shown exiting the biliary tree, with the Roux-en-Y jejunal limb prepared for the hepaticojejunostomy. C. Completed repair showing the silastic biliary stent traversing the liver and the hepaticojejunostomy. The Roux-en-Y jejunal limb has been brought to the hepatic hilum in retrocolic position. (Reproduced with permission from Cameron JL: Atlas of Surgery, Vol. I. Hamilton, Ontario, Canada: BC Decker; 1990.)
In the postoperative period, silastic stents are left to external gravity drainage. A cholangiogram is then performed on postoperative day 4 or 5 (Fig. 64-17). If the biliary tree is adequately decompressed and no leakage is seen, the stents can be internalized, and the perianastomotic drain is removed.

**FIGURE 64-17** Postoperative cholangiography after hepaticojejunostomy via percutaneous silastic biliary stents; the image shows no evidence of anastomotic leak.

The length of postoperative transanastomotic stenting is dependent on the individual patient, the clinical setting, and surgeon preference. Long-term stenting involves fluoroscopic exchange of stents at regular 2- to 3-month intervals. Timing of stent removal can be aided by biliary manometric flow studies that give objective data about the adequacy of the anastomosis, or by passing a clinical trial with the stent placed above the anastomosis.\(^{76}\)

An alternative described approach of doing a hepaticojejunostomy
involves an anterior longitudinal opening created in the bile duct and a long side-to-side anastomosis performed. Often this is done to the extrahepatic portion of the left hepatic duct after it is lowered by dividing the hepatic plate (Hepp-Couinard approach). This approach is particularly suitable for injuries at or just below the bifurcation. Right ducts do not lend themselves to this approach as well, since they have a short extrahepatic length. Sometimes the end of the right duct is used. However, dissection of the left duct provides a guide to the coronal plane in which the intrahepatic right hepatic ducts will be found and may further be exposed by removing liver tissue. During these procedures, exposure can be improved by dividing the bridge of tissue between segments III and IV and opening the gallbladder fossa. Finally, if still more exposure is needed, then resecting part of segment IVb and V will open the upper porta hepatis. The technique can avoid the need for postoperative stenting. Results of the Hepp-Couinard technique show that, at a mean follow-up of 4.9 years, anastomotic function was achieved in 96% of patients with stricture in only 5 patients; however, no reoperations were required for the recurrent stricture.  

Nonoperative Therapy. Nonoperative interventional radiology and endoscopic techniques have also been developed for the management of select patients with bile duct strictures and injuries. The most common nonoperative technique in these patients is interventional radiologic percutaneous stenting and balloon dilatation, which may be possible in patients with intact biliary-enteric continuity. With the administration of conscious sedation, the proximal biliary tree is accessed so that the stricture can be traversed using a guidewire under fluoroscopic guidance (Fig. 64-18). Angioplasty-type balloon catheters are used to perform dilatation of the stricture to a goal diameter based on the stricture location and the normal bile duct diameter. Following dilatation, a transhepatic biliary stent is left in place across the stricture. The stent allows for future cholangiography, repeat dilatation, and maintenance of the lumen while the bile duct heals. Complications of balloon dilatation occur in up to 16% of patients and include cholangitis, hemobilia, and bile leaks. Percutaneous management may still require repeated dilatations.
Results for the treatment of bile duct strictures using percutaneous balloon dilatation have improved. In a retrospective review, 109 patients with benign bilioenteric strictures were treated with percutaneous transhepatic balloon dilatation. The biliary drains were removed when no residual balloon waists were observed on at least 2 consecutive sessions, 6 weeks apart. Only 15% had recurrent biliary obstruction over a median follow-up of 59 months. Another study showed that percutaneous biliary dilatation was successful in
73% of patients after the first treatment. These results would appear comparable to other series in the current laparoscopic cholecystectomy era. However, the follow-up in most studies was less than 3 years, which is insufficient to make a definitive comment regarding long-term efficacy.

A series of 51 patients undergoing percutaneous balloon dilatation therapy for bile duct strictures following laparoscopic cholecystectomy was reported by Misra and associates. At a median follow-up of 76 months, overall success with balloon dilatation, defined as stent-free without the need for further intervention, was 58%. With additional stenting and balloon dilatation for 2 patients and surgical reconstruction for the remaining patients, all but 1 patient (98%) had a successful long-term outcome. These results suggest that in highly selected patients, percutaneous balloon dilatation can provide long-term successful results.

Endoscopic balloon dilatation has a more limited application, since it is technically possible only in patients with primary bile duct stricture repair or with choledochoduodenal anastomosis. Endoscopic retrograde cholangiography is performed, followed by endoscopic sphincterotomy. Sequential balloon dilatation is performed after the stricture is traversed by a guidewire, often with 1 or more endoprostheses left in place after dilatation. Complications associated with stent placement include cholangitis, pancreatitis, stent occlusion, migration, dislodgment, and ductal perforation and have a reported incidence between 9% and 60%.

Repeat cholangiography, often with repeat dilatations, may be performed at regular intervals of every 3 to 6 months. While most endoscopists advocate regular follow-up and reevaluation of the stricture, the risks of stent occlusion and replacement need to be weighed against the risks and costs of the repeat procedures, and there is still some debate about timing of stent change to avoid occlusion. Bergman and associates demonstrated a 70% reobstruction rate with resultant jaundice or cholangitis when stents were not exchanged at 3-month intervals. In contrast, Cote and colleagues describe and advocate leaving the stents in place until patients are symptomatic.

In addition, the rate of stent occlusion appears to vary with the type of stent used. Metallic stents provide a longer period of patency than plastic stents for patients with malignant obstruction, and the indications for their use in patients with benign strictures have increased. Some metallic stents cannot be routinely exchanged or removed, and several studies have
demonstrated high reocclusion rates at long-term follow-up. Newer self-expandable covered metallic stents provide a suitable alternative as they can be changed or removed after completion of treatment. 

While there have been no determinative studies for the length of time that stents should remain in place, most studies having excellent results have used larger bore stents (10 Fr or greater) left in place for 6 to 12 months. Long-term studies reporting the endoscopic treatment of benign bile duct injuries are few. One of the few studies that directly compared endoscopic therapy to surgical reconstruction was done by Pitt and colleagues from Indiana University. In 289 patients with bile duct injury, 70 (24%) were managed by interventional radiologists, 115 (40%) by endoscopists, and 104 (36%) by surgeons. Endoscopic therapy and interventional therapy consisted of dilatation and placement of an endoprosthesis. In addition, patients treated by endoscopy had a median of 3 stent exchanges. Surgical repair consisted of primarily biliary-enteric anastomosis or end-to-end repair. Surgery was associated with successful outcome in 88% of patients compared with 76% of patient treated endoscopically and 50% of patient treated by interventional radiology with a mean follow-up of 48 months. Outcomes were best for patients who had stents for greater than 6 months. Recurrent strictures after stent removal in several other series have been reported to occur at a rate varying from 0% to 20% at median follow-up of 29 to 108 months.

**OPERATIVE RESULTS**

Biliary injury and stricture repair is associated with significant morbidity and mortality. With improved medical technology and experience, the incidence of operative mortality has decreased markedly. A series of 200 consecutive patients repaired at the Johns Hopkins Hospital reported a perioperative mortality of only 1.7%. Advanced age, comorbid disease, and a history of major biliary tract infection are factors associated with operative mortality. Underlying liver disease is the most important correlated factor for operative mortality and morbidity, with advanced biliary cirrhosis and portal hypertension having mortality rates approaching 30%. Fortunately, in the modern era, such advanced disease is uncommon.

However, the effect of bile duct injuries on long-term life expectancy is a point of concern. An analysis of Medicare claims patients examined mortality associated with major bile duct injuries over an 8-year period in 791 elderly
patients and demonstrated a perioperative mortality of 2.7% associated with
repair. In addition, the study demonstrated that the adjusted hazard ratio for
dead during the follow-up period was significantly higher for patients with a
bile duct injury than in patients without a bile duct injury. The hazard
increased with advancing age and comorbidities and decreased with
experience of the repairing surgeon. The adjusted hazard for death during
follow-up was 11% greater if the repairing surgeon was the same as the
injuring surgeon. This study gives supportive evidence for improved survival
in patients with major bile duct injuries treated by experienced hepatobiliary
surgeons at tertiary referral centers.

A recent 5-year review of the New York SPARCS administrative database
detected 125 common duct injuries out of 156,958 laparoscopic
cholecystectomies with no mortalities within 30 days of the operation. However, the all-cause mortality was 20.8%, with a mean time to death of
1.64 ± 1.08 years. Significant factors predictive of all-cause mortality
included age >61 years, Medicare insurance, male sex, white race, diabetes,
hypertension, and pulmonary complications following surgery. Timing and
type of operative intervention did not influence mortality.

In most series, postoperative morbidity rates are in the range of 20% to
40%. Morbidity nonspecific to biliary surgery includes hemorrhage,
infection, and risks associated with general anesthesia. Complications
specific to biliary repairs include anastomotic leak, cholangitis, and hepatic
insufficiency associated with preexisting liver disease. Anastomotic leaks can
typically be managed via nonoperative means, especially when
transanastomotic stenting has been used. Percutaneous transhepatic stenting
may also have specific morbidity, including bile leaks from hepatotomy sites,
hemobilia, and cholangitis from stent occlusion.

The series reporting the outcomes in 200 patients undergoing surgical
reconstruction demonstrated a 43% overall postoperative complication rate.
The most common complications were wound infection (8%), cholangitis
(6%), minor stent-related complications (6%), and intra-abdominal
abscess/biloma (3%). Postoperative cholangiography revealed an anastomotic
leak in 4.6% of patients and extravasation at the liver dome–stent exit site in
10.3% of patients. These complications were all managed conservatively with
either new biliary stent placement or biliary stent exchanges, which were
required in 2.3% of patients. Postoperative percutaneous abscess/biloma
drainage was required in 9 patients (5.1%). No patients required reoperation
in the postoperative period. Despite the relatively high morbidity rate, median length of stay was similar to that in other reports (8 ± 4.6 days).

There are mixed results with respect to perioperative complications when vascular injury has occurred in association with a bile duct injury.\(^73,90,91\) A report from Schmidt and associates\(^90\) reported that a repair in the presence of uncontrolled infection, a concurrent hepatic artery injury, and injury level (at or above the bifurcation) were independent predictors of the development of major biliary complications. Another recent study showed that adequate sepsis control and delayed repair of biliary injuries should be considered for patients presenting between 8 days and 6 weeks after injury to prevent complications, especially if previous bile duct repair was attempted.\(^92\)

The ultimate goal of the repair of a bile duct stricture is a successful repair with no further symptoms, including jaundice, cholangitis, and preserved liver function. Excellent long-term results following operative repair of postoperative bile duct injuries after open cholecystectomy have been reported, with approximately 80% to 90% having a successful outcome (Table 64-4).\(^68,92-99\) Early reports and observations from the laparoscopic era were less favorable than those previously reported with open cholecystectomy repairs. Stewart and Way\(^74\) reviewed 85 patients who had undergone 112 biliary repairs and defined 4 factors that influenced success or failure of operative repairs after laparoscopic cholecystectomy bile duct injury: (1) performance of preoperative cholangiography, (2) choice of surgical repair, (3) details of surgical repair, and (4) experience of the repairing surgeon. Procedures without preoperative cholangiography were unsuccessful 96% of the time, and those with incomplete cholangiography data had a success rate of only 31%. With complete cholangiography data, the success rate was 84%. All patients with complete transection of the bile duct who underwent primary end-to-end repair over a T-tube had a failed result. In contrast, 63% of Roux-en-Y hepaticojejunostomy repairs were successful. Initial repair by the original laparoscopic surgeon was successful in only 17% of cases. Repeat attempts at repair by the same surgeon were never successful. Finally, patients whose first repair was by a tertiary care biliary surgeon achieved a 94% success rate.

**TABLE 64-4: RESULTS OF SURGICAL REPAIR OF POSTOPERATIVE BILE DUCT STRICTURES**
A series providing long-term results after repair of bile duct injuries and strictures in the 1990s was reported by Lillemoe and associates. A total of 156 consecutive patients underwent surgical reconstruction with a mean follow-up period of 57.5 months (range, 11-119 months; median, 54.7 months). The original operation consisted of laparoscopic cholecystectomy in 118 patients (76%), open cholecystectomy in 27 patients (17%), open cholecystectomy with bile duct exploration in 4 patients (3%), or other abdominal surgery or trauma in 7 patients (4%). Sixty patients (41%) had a previous attempt at repair prior to referral, with 8 patients (5.5%) having more than 1 attempt at repair prior to referral. Of the 156 operatively repaired patients, 142 patients had completed treatment at the time of final evaluation, with an overall success rate of 91%. Even though they were more likely to have had repair prior to referral and higher and more complex injuries, patients with repair of a stricture or injury associated with laparoscopic cholecystectomy had a better success rate than repair after other operations (94% vs 80%; \( P < .05 \)). There were 13 failures following surgical reconstruction. Ten patients had successful results following either surgical revision (1 patient) or percutaneous balloon dilatation (9 patients), resulting in an overall success rate of 98% including secondary intervention. Only 3 patients continued to require long-term biliary stents to prevent biliary obstruction symptoms and/or cholangitis. Comparable results have been reported from other high-volume hepatobiliary centers with similar volume of patients in the series. Outcomes after surgical repair for laparoscopic
cholecystectomy injury from other series are outlined in Table 64-5.92,97,99-103

TABLE 64-5: SURGICAL REPAIR OF LAPAROSCOPIC CHOLECYSTECTOMY BILE DUCT INJURIES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients</th>
<th>Bismuth Level III to V (%)</th>
<th>Success Rate (%)</th>
</tr>
</thead>
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<td>Dominquez-Rosado et al92</td>
<td>614</td>
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<td>Pitt et al68</td>
<td>104</td>
<td>93</td>
<td>88</td>
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<tr>
<td>AbdelRafey et al99</td>
<td>120</td>
<td>100</td>
<td>88</td>
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<tr>
<td>Lillemoe et al97</td>
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<td>Walsh et al100</td>
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<td>Mirza et al102</td>
<td>52</td>
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<tr>
<td>Nealon et al103</td>
<td>23</td>
<td>26</td>
<td>100</td>
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</tbody>
</table>

EFFECT OF SURGICAL REPAIR ON QUALITY OF LIFE

Despite the overall high level of success in the surgical management of laparoscopic cholecystectomy bile duct injuries, there is an impression that patients may have an impaired quality of life even after a successful repair of their bile duct injury. Quality of life after laparoscopic cholecystectomy bile duct injury has been addressed in several recent reports, with differing results.104-108 Two studies using the Short Form Health Survey quality-of-life instrument (SF-36) in patients with laparoscopic cholecystectomy injury found both the physical and mental quality of life aspects to be reduced compared to controls at approximately 5 years of follow-up.104,105 A study using the SF-36 found that patients with laparoscopic bile duct injury and subsequent biliary reconstruction had quality of life similar to matched controls and national norms in all 8 quality-of-life areas.106 Melton and associates105 assessed quality of life in 54 patients who underwent successful surgical repair of laparoscopic cholecystectomy bile duct injuries and compared these results to quality-of-life measures in patients after
uncomplicated laparoscopic cholecystectomy and in healthy controls using a standard quality-of-life instrument, which was used to assess the physical, psychological, and social domains of health-related quality of life. Patients after surgical repair had overall quality-of-life scores comparable to those of controls. Only in the psychological dimension were patients post–bile duct injury repair found to have significantly worse scores compared to controls. Patients who reported pursuing a lawsuit following their injury (31%) had significantly worse quality-of-life scores in all domains when compared to those who did not entertain legal action ($P < .01$). A recent study using the SF-36 found that quality of life improves significantly after the first year of surgical repair, reaching a plateau at 5 years. There was no difference in life summary scores from 5 years to 10 years after repair.\textsuperscript{108}

**Summary**

Postoperative bile duct strictures and major injuries remain a considerable surgical challenge. With proper diagnostic workup, clinical optimization, and definitive treatment, the vast majority of patients can achieve satisfactory outcomes. With success rates of over 90% at long-term follow-up, the gold standard for managing patients with major bile duct injuries and strictures in the current era remains surgical reconstruction. In select patients with biliary-enteric continuity, percutaneous or endoscopic management with balloon dilatation may be an appropriate alternative, with success rates of approximately 50% at long-term follow-up.

**INFLAMMATORY CAUSES OF BILIARY STRICTURE**

Biliary strictures may occur in association with a wide range of processes causing fibrosis of the bile ducts. While inflammatory causes of bile duct strictures account only for a minority of biliary strictures in the United States, biliary strictures from these causes are important diagnostic and therapeutic challenges. Strictures from chronic pancreatitis, biliary calculous disease, sphincter of Oddi stenosis, and peptic ulcer disease can usually be managed with choledochoduodenostomy or Roux-en-Y hepaticojejunostomy without long-term stenting. The management of other infrequent causes of benign
biliary strictures depends on the etiology, natural history, and severity of disease.

**Chronic Pancreatitis**

Chronic pancreatitis is an infrequent cause of bile duct stenosis and stricture, accounting for less than 10% of benign biliary strictures. While acute pancreatitis is frequently associated with transient partial obstruction of the distal common bile duct from inflammation and edema, chronic pancreatitis can result in distal bile duct obstruction from inflammation and parenchymal fibrosis of the pancreatic gland. Strictures from chronic pancreatitis typically involve the entire intrapancreatic segment of the common bile duct, resulting in proximal dilatation of the biliary tree.

Chronic pancreatitis resulting in bile duct stricture is most commonly caused by alcoholism. Strictures more commonly present in patients that have advanced disease with pancreatic calcification, diabetes, or malabsorption at the time of presentation. The exact incidence of common bile duct strictures in patients with chronic pancreatitis increased because cholangiography is more routinely performed. With a review of several studies, common bile duct strictures associated with chronic pancreatitis occur in approximately 8% of patients, with estimated ranges varying from 3% to 46% of patients.\textsuperscript{109-111}

Common bile duct strictures due to chronic pancreatitis may have a wide range of clinical presentations. On one end of the spectrum, patients can be asymptomatic with only abnormal liver function tests. Serum alkaline phosphatase, the most sensitive liver function test, is elevated in over 80% of cases. Patients can also present with abdominal pain with or without jaundice. Importantly, abdominal pain from biliary strictures can be difficult to distinguish from pain caused by chronic pancreatitis. Patients with pain from biliary strictures that are not properly diagnosed and treated may undergo inappropriate and unsuccessful operative procedures to address pain presumed to be from chronic pancreatitis. Finally, patients who develop jaundice in the setting of chronic pancreatitis may present a diagnostic dilemma, as an underlying peri-ampullary malignancy must also be considered.\textsuperscript{112}

Evaluation of bile duct strictures from chronic pancreatitis is most
effectively accomplished with cholangiography. MRCP is the preferred route for noninvasive assessment, with both ERCP and PTC effective at delineating anatomy and allowing decompression of the biliary tree in the setting of cholangitis or severe jaundice. ERCP is the preferred diagnostic procedure because it has the advantage of demonstrating pancreatic ductal anatomy, including possible abnormalities, which are especially useful in surgical management. The most common cholangiographic image in chronic pancreatitis–associated bile duct strictures is a long (usually 2-4 cm), smooth, gradual tapering of the distal common bile duct (Fig. 64-19).

FIGURE 64-19 Stricture from chronic pancreatitis involving the entire

There has been a gradual evolution in the endoscopic management of distal biliary strictures secondary to chronic pancreatitis. Most early series used single (usually 10 Fr) plastic stents for varying time periods. Long-term stricture resolution occurred in only approximately 25% of patients, and stent-related complications were high if stent exchanges were not performed routinely every 3 to 4 months. Recent studies show that either multiple plastic stents or self-expanding covered metallic stents produce resolution in 90% of patients at 12 months of follow-up.\(^{85,113,114}\)

The most common accepted indications for operative management in common bile duct strictures from chronic pancreatitis are cholangitis, jaundice, or significant pain. It remains unclear, however, if biliary decompression in asymptomatic patients with elevated serum alkaline phosphatase is indicated. Many surgeons do advocate biliary bypass in this situation, as early biliary cirrhosis changes may be observed in liver biopsy specimens in patients with long-standing, significant biliary obstruction from chronic pancreatitis.\(^{115}\)

Biliary bypass with choledochoduodenostomy or Roux-en-Y choledochojejunostomy represents the optimal form of management for bile duct strictures associated with chronic pancreatitis. Potential advantages of choledochoduodenostomy over Roux-en-Y choledochojejunostomy include maintenance of bile flow into the duodenum that may be more physiologic, increased technical ease, and no loss of small bowel length for formation of a Roux-en-Y limb. Operative management with pancreaticoduodenectomy is appropriate in patients in whom periampullary malignancy cannot be ruled out by imaging studies or clinical course or in those patients with significant pain attributed to proximal pancreatic duct disease. Both long-term and short-term outcomes of surgically managed distal bile duct strictures from pancreatitis are usually excellent.\(^{116,117}\)

The management of common bile duct strictures from chronic pancreatitis with either transduodenal sphincterotomy or endoscopic sphincterotomy is not recommended due to the stricture’s long length. While long-term follow-up is lacking, several series have reported success in 60% of patients with
follow-up at approximately 2 years after endoscopic balloon dilatation of distal bile strictures from chronic pancreatitis.\textsuperscript{118} It would appear that in most cases when a benign process can be expected to require years of follow-up that surgery would be the best form of management.

**Gallstone Disease**

Long-standing cholelithiasis with recurrent bouts of cholecystitis results in a progressively fibrosed, shrunken gallbladder. Eventually, the gallbladder lumen can lie alongside the common hepatic duct, resulting in inflammation and resultant bile duct stricture. Often referred to as Mirizzi syndrome, this process is typically subdivided into 2 categories. Type I Mirizzi syndrome occurs when the process results in either mechanical compression of the duct or an inflammatory stricture of the common hepatic duct. In contrast, type II consists of erosion of the stone in the duct, resulting in cholecystocholedochal fistula.

Mirizzi syndrome usually presents as jaundice or recurrent cholangitis. In some long-standing cases, these findings exist in the face of chronic gallbladder symptoms. In cases of Mirizzi syndrome associated with acute cholecystitis, care must be taken at the time of cholecystectomy to avoid bile duct injury during initial dissection. The presence of Mirizzi syndrome obliterates the triangle of Calot and makes laparoscopic cholecystectomy particularly difficult and will often require conversion to an open procedure. If Mirizzi syndrome is considered, intraoperative cholangiography should be performed.

If urgent cholecystectomy is not indicated, ERC or PTC can help to delineate the anatomy. Importantly, Mirizzi syndrome can be difficult to distinguish from strictures that result from gallbladder cancer or cholangiocarcinoma.\textsuperscript{119} ERC can also be helpful for obtaining brush biopsies in these patients.

Formal management of strictures from biliary stones varies according to the extent of disease. Patients in whom the bile duct is inflamed and no fistula is present (type I) can often be managed with cholecystectomy. The common hepatic duct almost always returns to normal after the offending stone has been removed by cholecystectomy and the inflammatory process has resolved. Care must be taken, however, during the dissection to avoid
creating a defect in the common hepatic duct. Rarely, after the acute episode has resolved, a well-established stricture presents months to years after the acute episode. In such cases, management by Roux-en-Y hepaticojejunostomy is appropriate. If a cholecystocholedochal fistula (type II) is present, partial cholecystectomy is recommended, and the cuff of remaining gallbladder is used to repair the bile duct over a T-tube.

In addition to Mirizzi syndrome, calculous disease also rarely results in strictures due to choledocholithiasis. The pathogenesis of strictures from choledocholithiasis is thought to be from epithelial erosion of the distal bile duct from calculous disease, resulting in inflammation with subsequent fibrosis and stricture.

Nearly all stones remain entrapped in the intrapancreatic portion of the common bile duct because of the anatomic tapering of the common bile duct. These trapped stones are often difficult to remove via endoscopic means or via a supraduodenal approach during common bile duct exploration. In fact, common bile duct exploration to retrieve stones with forceps, scoops, and catheters can often result in additional trauma to the friable distal duct from excessive intraoperative manipulation. After stone removal, the distal bile duct should be gently sized with a soft rubber catheter to check for the presence of a stricture. Strictures often may not be recognized until the postoperative period when T-tube cholangiography is performed. When strictures are found postoperatively, stricture repair should be performed after inflammation has resolved, typically after 4 to 6 weeks. Stricture repair of the distal bile duct is indicated for persistent strictures using either Roux-en-Y choledochojejunostomy or choledochoduodenostomy biliary-enteric anastomosis. A choledochoduodenal anastomosis is preferable in patients with a large, dilated (>2 cm in diameter) proximal duct because of its technical ease and excellent results.

**Recurrent Pyogenic Cholangitis and Other Parasitic Disease**

Recurrent pyogenic cholangitis, also known as Oriental cholangiohepatitis, is endemic in Southeast Asia. Recurrent pyogenic cholangitis occurs infrequently in Western countries, but with immigration from Asia, it is now increasingly encountered. Most cases are due to parasitic infection (*Ascaris*...
*lumbricoides* or *Clonorchis sinensis*) of the biliary tree. The infection results in biliary stasis, bacterial overgrowth and inflammation, biliary sludge, and brown (calcium bilirubinate) stone formation. Patients will typically have multiple intrahepatic and extrahepatic stones and strictures, as well as recurrent cholangitis. Although strictures can occur throughout the biliary tree, they are most common in the main hepatic ducts, with disease in the left hepatic duct typically more frequent and more severe than the right.

Classically, patients are young, thin, and of Asian descent and present with recurrent bouts of cholangitis. Cholangitis can range in severity from subclinical chronic illness to life-threatening acute suppurative cholangitis.

Diagnostic imaging modalities for Oriental cholangiohepatitis include ultrasonography, CT scan, MRCP, ERC, and PTC. Although ultrasound is poor at showing biliary strictures reliably, it is effective at demonstrating biliary obstruction, biliary tract stones, pneumobilia from gas-forming organism infection, and liver abscesses. Intrahepatic stones on ultrasound have a characteristic posterior acoustic shadowing. CT scan is useful for delineating hepatic anatomy and parenchymal involvement in more advanced disease, which is helpful for guiding potential liver resection. MRCP should be the first step to noninvasively define the biliary anatomy for the presence of strictures and stones. In addition, ERCP and PTC provide therapeutic biliary decompression in the setting of acute cholangitis (*Fig. 64-20*).
Long-term management of recurrent pyogenic cholangitis is aimed at treating biliary strictures using improved biliary drainage via biliary reconstruction. Following temporary decompression of the biliary tree with ERCP or PTC for acute cholangitis, patients are allowed a period of several weeks for clinical optimization prior to further management. Attempts at percutaneous or endoscopic manipulations of the biliary tree for stone extraction and biliary stricture dilatation may be entertained. These interventions, however, have only temporary short-term benefit, and operative management will eventually need to be considered.

Standard operative management consists of Roux-en-Y hepaticojejunostomy, usually with a transhepatic stent. An attempt at
complete clearance of stones from the intrahepatic ducts should be made, including the use of choledochoscopy. The stent is useful for follow-up cholangiography and further stone clearance after the initial procedure. Another option for follow-up management is for the blind end of the Roux-en-Y limb to be sutured to the peritoneal surface of the abdominal wall, along with a radiopaque marker. This creates an enteric portal for future access to the biliary tree and anastomosis. In cases in which disease is confined to one portion of the liver with extensive fibrosis or hepatic abscess, hepatic resection may be considered.

Other causes of biliary strictures from parasites include various forms of echinococcal disease. Biliary strictures from echinococcal infection are primarily related to the compression of bile ducts by a thick-walled cyst. Because of its low rate of morbidity, long-term endoscopic stent therapy has become the initial therapy of choice in patients with biliary stricture from hydatid disease. Operative therapy should be considered only in cases of failed previous repairs or failed endoscopic therapy. Surgical treatment of echinococcal liver and biliary disease is associated with a high rate of postoperative bile duct stricture, necessitating long-term clinical surveillance.

**Sphincter of Oddi Stenosis**

Also referred to as papillitis, stenosis of the sphincter of Oddi is a benign intrinsic obstruction of the common bile duct outlet. Papillitis is typically associated with inflammation, fibrosis, or muscular hypertrophy of the sphincter of Oddi. Patients with sphincter of Oddi stenosis are prone to (1) common bile duct obstruction from fibrosis and stenosis of the papilla, (2) recurrent pancreatitis, and (3) recurrent right upper quadrant abdominal pain in the absence of jaundice or pancreatitis. Initial presentation is most often jaundice or cholangitis. Patients can also sometimes present with an impacted stone at the ampulla.

The etiology of papillitis is unknown. Many cases are thought to be caused by trauma from the passage of multiple small stones or sludge from the common bile duct through the ampulla, resulting in inflammation, fibrosis, and stricture formation. There are other patients, however, who have papillary stenosis without gallstones. The cause in these cases is less clear; potential triggers include primary sphincter motility disorders and congenital anomalies.
Management consists of proper diagnostic imaging and therapeutic sphincterotomy. Cholangiography with MRCP, PTC, or ERCP is the mainstay of diagnostic imaging. Therapeutic sphincterotomy can be performed either endoscopically or operatively in conjunction with cholecystectomy. The procedure of choice in patients with previous cholecystectomy is endoscopic sphincterotomy.\textsuperscript{122}

**PRIMARY SCLEROSING CHOLANGITIS**

PSC is an idiopathic condition characterized by a progressive, chronic cholestatic process resulting in diffuse inflammation, sclerosis, and obliteration of the intrahepatic and extrahepatic biliary duct systems and subsequently leading to liver cirrhosis. The diagnosis of PSC is confirmed by cholangiography, with findings of multiple areas of stricture and dilatation.

PSC has a variable course but can progress to biliary obstruction with secondary liver cirrhosis, portal hypertension with bleeding varices, or hepatic failure. Finally, PSC is a strong risk factor for the development of cholangiocarcinoma. Surgical management for symptomatic disease in patients with primarily extrahepatic and/or hilar disease and with no evidence of cirrhosis includes resection of the hepatic bifurcation with long-term transhepatic stenting. Finally, liver transplantation is the treatment of choice in patients with primarily intrahepatic strictures or advanced cirrhosis.

**Pathogenesis**

The etiology of PSC remains unknown, and a variety of causal theories have been proposed. Inflammatory bowel disease, particularly ulcerative colitis, is present in 30% to 90% of patients with PSC in several large population-based studies.\textsuperscript{123,124} This tight association with inflammatory bowel disease suggests an autoimmune process. However, other mechanisms likely have a role in pathogenesis since only a minority with ulcerative colitis have PSC.\textsuperscript{123} Although both ulcerative colitis and PSC may occur in the same individual, the 2 disorders may occur at different times. PSC, for example, may occur years after colectomy for ulcerative colitis. In addition to commonly occurring in patients with ulcerative colitis, PSC can occur with multifocal fibrosclerosis syndromes, including retroperitoneal, mediastinal, and/or
periureteral fibrosis, Riedel thyroiditis, or pseudotumor of the orbit.

Due to the association between PSC and inflammatory bowel disease, several investigators have speculated that increased bacterial spread into the portal circulation from inflamed large or small intestine may lead to chronic or recurrent cholangitis. In support of this, an animal model of small intestinal bacterial overgrowth has biliary findings similar to PSC. Although some studies have documented increased portal bacteremia in patients with PSC, other studies have not confirmed this finding.

Correlating evidence for an immunologic cause of PSC includes its association with hypergammaglobulinemia (30%) and an increase in IgM (50%). Patients with PSC can also have autoantibodies, with titers in the range associated with autoimmune hepatitis. In particular, anti–smooth muscle antibodies and antinuclear antibodies are present in approximately 75% of patients. Other autoantibodies commonly associated with the disease include cytoplasmic and nuclear antigens to neutrophils (perinuclear antineutrophil cytoplasmic antibodies [p-ANCA]). The autoantibody p-ANCA is often found in patients with PSC and no ulcerative colitis but is uncommon in patients with ulcerative colitis alone.

Several genetic factors appear to give individuals a predisposition to PSC, including increased prevalence of HLA-B8, -DR3, and -Drw52a. The HLA-B8 and HLA-DR3 haplotypes are associated with other autoimmune diseases, including celiac disease, myasthenia gravis, and diabetes mellitus. A specific mutation of MICA (a major histocompatibility complex class I–related molecule) is also strongly associated with PSC (58% vs 22% in controls).

In contrast to PSC, secondary sclerosing cholangitis has similar clinical characteristics but has identifiable causes. The inciting factors for secondary sclerosing cholangitis include infectious cholangiopathy associated with acquired immunodeficiency syndrome, congenital biliary abnormalities, ischemic cholangiopathy secondary to intrahepatic arterial infusion of fluorouracil, hepatic allograft rejection, graft-versus-host disease in bone marrow transplantation, collagen vascular diseases, histiocytosis X, sarcoidosis, and mast cell cholangiopathy. Patients with diffuse stricturing from fluorouracil are managed by simple discontinuation of infusion and, in some cases, percutaneous transhepatic drainage. Surgery should be reserved for patients with persistent evidence of biliary obstruction. The pathogenesis
of acquired immunodeficiency syndrome cholangiopathy is believed to be viral and related to cytomegalovirus infection. No experience in the surgical management of this condition has been reported.

**Presentation**

PSC is predominantly a disease of young men. Approximately 70% of patients are male, and the average age at the time of diagnosis is 40 years. The typical presentation includes either an asymptomatic individual with abnormal liver function tests or an individual with intermittent jaundice. Other common symptoms may include right upper quadrant pain, weight loss, fever, pruritus, and fatigue. Despite its name, a minority have acute cholangitis, blood cultures are rarely positive, and approximately 10% are very symptomatic at the time of diagnosis; however, asymptomatic patients can have deceptively advanced disease.

**Diagnosis**

Lab tests with PSC typically reveal a cholestatic picture. Patients will have an elevated alkaline phosphatase, and during exacerbations, they may have elevated bilirubin. Early in the disease course, patients will have a normal albumin. The diagnosis is usually made through cholangiography, usually MRCP or ERCP. The typical study reveals multifocal strictures and dilatations, referred to as “beading,” of the intrahepatic and extrahepatic ducts (Fig. 64-21). The therapeutic modality of choice for cases requiring intervention is via the endoscopic route. PTC may be difficult since cannulation of nondilated and fibrotic ducts associated with PSC can be technically challenging via this approach. At the time of diagnostic cholangiography, brushings for cytology should be obtained to help distinguish between benign and malignant strictures.
Management

Management of PSC has several important treatment goals, including halting or reversing the disease process, managing disease progression, and symptom control. Unfortunately, there are no effective medical treatments that slow the progression of PSC. Patients should be monitored closely with cholangiography, liver biopsy, and cytologic brushings to detect disease progression and development of malignancy or biliary cirrhosis.

Most medical therapies are aimed at symptomatic relief or antibiotic
treatment in the setting of cholangitis. Immunosuppression with glucocorticoids, methotrexate, azathioprine, 6-mercaptopurine, tacrolimus, or cyclosporine has not demonstrated efficacy for disease progression or survival. The use of ursodeoxycholic acid (UDCA) has demonstrated improvement of liver function tests and symptoms. A prospective, randomized, placebo-controlled trial of UDCA, however, did not demonstrate long-term clinical benefit with this agent.\textsuperscript{131} High-dose UDCA in several small pilot studies has demonstrated decreased disease progression and improved survival\textsuperscript{131-133}; larger-scale prospective trials with high-dose UDCA are still ongoing.

A dominant extrahepatic biliary stricture (a high-grade, localized area of narrowing) occurs in approximately 20\% of patients with PSC. These patients can be managed potentially with endoscopic therapy using dilatation with or without stenting. Cytologic brushings at the time of endoscopy should also be obtained to investigate for cholangiocarcinoma. Several retrospective reports have demonstrated benefit in relieving symptoms and improving liver function tests from endoscopic therapy and possible delay in disease progression.\textsuperscript{134} However, the durability of endoscopic therapy appears to be poor, with most patients requiring repeat dilatations at regular intervals. Whether patients should undergo stenting at the time of dilatation is not clear, with short-term results of stenting similar to those of dilatation treatment alone\textsuperscript{134,135} and with no long-term outcomes at present comparing the 2 techniques.

Operative biliary reconstruction with transhepatic stenting for primarily extrahepatic and/or hilar disease in noncirrhotic patients has been demonstrated to have excellent long-term outcomes.\textsuperscript{134,135} Ahrendt and associates\textsuperscript{136} reported 146 patients with PSC managed with either biliary reconstruction or nonoperative biliary dilatation. Survival was significantly longer in noncirrhotic patients with PSC managed surgically compared to patients managed nonoperatively, and time before requiring liver transplantation was significantly longer in the surgically managed patients (Fig. 64-22).
The natural history of PSC is typically progressive. Regardless of therapy, median survival is typically 12 years after diagnosis. Survival is significantly worse in patients symptomatic at the time of diagnosis. The incidence of cholangiocarcinoma of PSC patients at 5 years is 10% to 15%, and at 10 years, it increases to 30%.

Hepatic transplantation provides excellent results in patients with PSC and end-stage liver disease, with 5-year actuarial survival and graft functioning of 85% and 72%, respectively. Liver transplantation should be considered in patients with sclerosing cholangitis before the disease is too advanced. Primary indicators for referral for liver transplantation include persistently elevated bilirubin or decreased quality of life from disabling fatigue, severe pruritus, muscle wasting, or bacterial cholangitis. Biliary tract surgery prior to transplantation does not affect either short-term outcomes or survival following transplant.

Patients with preoperatively recognized cholangiocarcinoma have a poor prognosis. These patients are not appropriate candidates for transplantation.
On the other hand, the presence of a small (<1 cm) cholangiocarcinoma discovered incidentally on pathology at transplantation does not appear to portend a poor prognosis.

Patients transplanted for PSC are also at increased risk of postoperative biliary stricture compared to patients transplanted for other primary disease processes. Recurrent PSC occurs in approximately 20% of patients 5 years after transplantation, but with typically a less aggressive course.139

**SUMMARY**

PSC currently has no proven effective medical treatment. Resection of the hepatic duct bifurcation in conjunction with long-term transhepatic stenting in noncirrhotic patients with primarily extrahepatic and/or hilar disease can delay or even prevent the need for hepatic transplantation. This operation does not influence the outcomes associated with hepatic transplantation. Transplantation is recommended in patients with primarily intrahepatic strictures or advanced cirrhosis.

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INTRODUCTION

This chapter focuses on gallbladder cancer and cholangiocarcinoma, including intrahepatic, perihilar, and extrahepatic variants. Because the epidemiology, clinical presentation and surgical approach for these tumors are distinct, they are discussed separately.

GALLBLADDER CANCER

Epidemiology

With an incidence of approximately 3000 cases annually in the United States (incidence 1.14 per 1000,000 people), gallbladder cancer it accounts for only 0.5% of all gastrointestinal tract malignancies in this country. Incidence
increases with age and is two to three times higher in women than in men. Worldwide, the highest incidence rates (up to 8.0 per 100,000 in men and 22 per 100,000 in women) occur among populations in the Indian subcontinent, in the Western part of South America (eg, Colombia and Ecuador), and to a lesser extent in East Asia and Eastern Europe. In the United States, the incidence is higher in American Indians and in Hispanics.\textsuperscript{2,4} The best characterized risk factor for the development of gallbladder cancer is chronic inflammation associated with gallstones (Table 65-1). Although only a small fraction of patients with cholelithiasis will develop gallbladder cancer, gallstones are present in 70\% to 90\% of patients diagnosed with gallbladder cancer.\textsuperscript{4–6} Further, the geographic pattern of gallbladder cancer incidence correlates with that of cholelithiasis.

**TABLE 65-1: RISK FACTORS FOR DEVELOPING GALLBLADDER CANCER**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis</td>
<td>Porcelain gallbladder, adenomatous polyps of the gallbladder, chronic <em>Salmonella typhi</em> infection, carcinogens (eg, radon), abnormal pancreaticobiliary duct junction (APBDJ)</td>
</tr>
</tbody>
</table>

Other factors implicated to increase the risk of developing gallbladder cancer include porcelain gallbladder, adenomatous polyps of the gallbladder (in contrast, cholesterol and inflammatory polyps and adenomyomatosis are not believed to be the risk factors), chronic infection with *Salmonella typhi*, carcinogen exposure (eg, increased risk has been reported for miners exposed to radon), obesity, and abnormal pancreaticobiliary duct junction (APBDJ). In this latter condition, a long common channel, formed by an abnormally proximal junction between the pancreatic and common bile ducts (CBDs), and elevated sphincter of Oddi pressures create a predisposition to reflux pancreatic exocrine secretions into the bile ducts. APBDJ is most prevalent in Asian countries and appears to increase the risk of development of biliary cancers, especially gallbladder cancer.\textsuperscript{7} Gallbladder cancers arising in patients with APBDJ tends to occur at a younger age, to have a lesser degree
of female predominance, and to be less often associated with cholelithiasis than those arising in patients without APBDJ.

Pathogenesis and Pathology

Chronic inflammation of the gallbladder mucosa related to gallstones is hypothesized to be the major factor leading to malignant transformation in most cases of gallbladder cancer. The progression from dysplasia to carcinoma in situ (CIS), then to invasive cancer has been described for gallbladder cancer, although a less common pathway involves progression of adenomas to gallbladder cancer.\(^8\) Reports outlining the molecular changes associated with this progression are emerging: frequently altered genes include \(p53\), \(K\)-\(ras\), \(P16INK4A\), and \(ERBB2/HER2\).\(^9,10\)

Gallbladder cancers arising from adenomas may be associated with a distinct pathogenetic mechanism, especially when compared to those arising in patients with APBDJ. Adenomas have a high prevalence \(\beta\)-\(catenin\) mutations, whereas dysplastic lesions and cancers associated with APBDJ have a high prevalence of \(K\)-\(ras\) mutations and a low prevalence of \(\beta\)-\(catenin\) mutations. \(p53\) and \(P16INK4A\) mutations are not seen in adenomas or dysplastic lesions, and thus appear to be later events in gallbladder carcinogenesis.\(^10\)

Eighty percent of primary gallbladder cancers are adenocarcinomas. Other histological types include small cell cancer, squamous cell carcinoma, lymphoma, and sarcoma. Gallbladder cancers are also classified according to morphology as infiltrative, nodular, papillary, or a combination of these types. Papillary cancers tend to grow within the gallbladder lumen and are less likely to invade the liver or to metastasize to lymph nodes; they are associated with the best prognosis. Infiltrative or nodular cancers have a more diffuse pattern of growth that is difficult to recognize on imaging studies. These lesions are more likely to have invaded the liver and to have metastasized to lymph nodes by the time of diagnosis.

Clinical Presentation and Diagnosis

In the absence of advanced disease, patients with gallbladder cancer are asymptomatic or have symptoms such as abdominal pain, anorexia, nausea,
and vomiting that may be indistinguishable from those of cholelithiasis or cholecystitis. Due to these nonspecific symptoms, a diagnosis of gallbladder cancer is not made preoperatively in over half the cases and is often an unexpected finding on pathologic review of gallbladders removed for presumed benign (gallstone) disease. With advanced disease, patients can present with weight loss, obstructive jaundice (due to tumor invasion into the biliary tree or to liver metastases), and duodenal obstruction. Signs associated with advanced disease include palpable abdominal masses, hepatomegaly, and ascites.

Laboratory tests may suggest obstructive jaundice if this condition is present; otherwise, they are not helpful in the diagnosis of gallbladder cancer. Tumor markers such as carcinoembryonic antigen (CEA) or CA 19-9 may be elevated; however, they lack sufficient sensitivity or specificity to be useful in clinical decision-making for individual patients.

Patients with suspected gallstone- or gallbladder-related conditions typically undergo transabdominal ultrasonography (US). Findings suggestive of gallbladder cancer on ultrasonography include mural thickening or calcification, a gallbladder mass greater than 1 cm in diameter, and loss of the normal gallbladder wall–liver interface (Fig. 65-1). Relative to transabdominal ultrasonography, endoscopic ultrasonography (EUS) offers greater accuracy in assessing depth of gallbladder wall penetration by masses and regional lymph node enlargement and also may provide better characterization of gallbladder masses. As EUS is invasive and does not necessarily provide more clinically relevant information than other noninvasive imaging modalities, it is not widely utilized. EUS-guided biopsy, however, is an effective technique in cases in which a tissue diagnosis is required.
FIGURE 65-1 Ultrasound of gallbladder cancer. The images demonstrate asymmetric wall thickening of the body and neck of the gallbladder. (Used with permission from Dr. Steven E. Seltzer, Department of Radiology, Brigham & Women’s Hospital;
Cross-sectional imaging (ie, either computed tomography [CT] scanning or magnetic resonance imaging [MRI]) should be performed on patients suspected of having gallbladder cancer. CT is typically more widely available and less expensive than MRI. Findings of gallbladder cancer include a mass protruding into the gallbladder lumen or completely replacing the gallbladder and focal or diffuse thickening of the gallbladder wall (Fig. 65-2). CT scanning also offers information on the presence or absence of distant metastases, regional lymph node involvement, and local invasion into the liver and porta hepatis.

**FIGURE 65-2** CT scan of gallbladder cancer. The image shows a 3.5 × 4 cm lesion arising from the gallbladder fundus and extending into segment 5 of the liver.

MRI, particularly with magnetic resonance cholangiopancreatography (MRCP), can offer additional information on invasion into the liver. It is not known, however, whether routine MRI adds to the results obtained from CT
scan, and thus it should be used selectively, for instance when CT findings are equivocal or precise delineation of biliary anatomy is warranted. Endoscopic or percutaneous cholangiography is not indicated for diagnostic purposes, and is reserved for therapeutic purposes. Similarly, diagnostic angiography has been replaced by CT and MRI angiography, which provide detailed imaging of vessels in the porta hepatitis.

While fluorodeoxyglucose (FDG) positron-emission tomography (PET) has not been universally accepted as a part of the routine staging evaluation for gallbladder cancer, retrospective studies show that gallbladder cancer tends to be FDG-avid, and that when utilized PET is more sensitive than CT for the detection of distant metastases, and therefore alters management in a significant fraction of cases when used. PET is less useful in differentiating benign versus malignant disease, and therefore is limited in its ability to differentiate between residual disease and post-surgical changes after cholecystectomy. While some favor the routine use of PET, others favor using PET selectively to further evaluate indeterminate findings on CT or MRI.

Staging

Several staging systems for gallbladder cancer have been described. The Nevin staging system and the Japanese Biliary Surgical Society system are mainly of historical interest. The American Joint Committee on Cancer (AJCC) staging system, now in its eighth edition (Table 65-2), which is based on the tumor depth, regional nodal involvement, and the presence of distant metastasis (tumor-node metastasis [TNM]) is currently the most widely used staging system. The current AJCC staging system numbered stages are useful in determining prognosis as well as for guiding appropriate treatment according to current paradigms.

TABLE 65-2: TNM STAGING OF GALLBLADDER CANCER
Surgical Therapy

Surgical resection is the only known curative form of therapy for gallbladder cancer. For patients in whom surgical exploration is contraindicated because of medical comorbidities or due to metastatic or unresectable disease, a percutaneous or endoscopic needle biopsy can be obtained to confirm the diagnosis. For patients in whom surgery is planned, a preoperative biopsy is contraindicated, as gallbladder cancer has a propensity for dissemination along needle tracts.

Recommendations for surgical treatment according to disease stage are given below. Specific technical issues are discussed subsequently.

INCIDENTAL FINDINGS ASSOCIATED WITH RISK OF MALIGNANCY
Adenomas and gallbladder calcification have been associated with the risk of developing cancer or even harboring occult malignancy, and thus the management of these findings warrants specific discussion. While gallbladder polyps are noted in approximately 5% of patients undergoing gallbladder ultrasonography, not all polyps are adenomas. In fact, most are cholesterol polyps. Inflammatory polyps, hyperplastic polyps, and adenomyomatosis among other lesions can also appear as polypoid lesions in the gallbladder. Adenomyomatosis, which is an extension of Rokitansky-Aschoff sinuses through the muscular wall, can often be differentiated from adenomas by imaging, while distinction between adenomas and other polypoid lesions is more difficult. US can distinguish adenomyomatosis from other polypoid lesions in many cases, but occasionally axial imaging (CT or MRI) is needed. MRI is reported to be the most accurate imaging modality for making a diagnosis of adenomyomatosis. Of the polypoid lesions in the gallbladder, only adenomas harbor any malignant potential. In recent series of resected gallbladder polyps, less than 20% were found to be adenomatous, and the rate of malignancy was around 5% or less. Patients evaluated for gallbladder polyps should be assessed for symptoms attributable to the biliary system. While symptoms are rarely related to polyps, if another cause cannot be found, resection is warranted. The most consistent predictors of malignancy in polyps are older patient age and larger polyp size. Of these, size is particularly important as it is quite rare for malignancy to be identified in polyps <1 cm. Thus, size ≥1 cm is the most widely accepted indication for surgery. As the coexistence of gallstones also predicts malignancy in some studies, some authors advocate surgery in this setting. The finding of gallbladder polyps in patients with primary sclerosing cholangitis (PSC) warrants special consideration, as polyps in this setting are more likely to be neoplastic or even malignant. Several widely accepted consensus guideline advocate surgery for all polyps in patients with PSC, while some authors recommend mandate surgery only for patients with polyps ≥8 mm in size.

Patients with polypoid lesions of the gallbladder who do not undergo surgery should be followed with serial US unless a diagnosis other than adenoma is confirmed. Polyps that increase in size have a high chance of being neoplastic and should be resected. There are little data to guide the frequency and duration of surveillance. It is reasonable to obtain an US at 6 months, 1 year, and then yearly. As polyps <5 mm are most frequently non-
neoplastic, it is likely not necessary to follow these lesions beyond 1 year if they are stable in size.

The operative approach for the patient with a polypoid lesion of the gallbladder should be carefully considered. Until recently, an open approach was favored whenever the possibility of malignancy was considered. As the probability of malignancy is quite low in cholecystectomies performed for presumed gallbladder polyps, laparoscopic cholecystectomy is an appropriate treatment for early-stage (T1a) cancer (see below) and as the outcome for cancers confined to the gallbladder is not dramatically worse when laparoscopic cholecystectomy is performed as the initial treatment, it is reasonable to start with a laparoscopic approach in selected cases. The patient needs to be aware that if malignancy is found, open exploration an extended resection may be indicated (see below). This can be performed in the same setting based on frozen section results. The laparoscopic approach should be reserved for cases where the preoperative imaging does not indicate features suggestive of malignancy. Similarly, if on preoperative imaging the mass is adjacent to the liver hilus, stronger consideration should be given to initial en bloc resection of the gallbladder with the cystic plate of the liver (see below). Lastly, there should be a low threshold for conversion to an open approach (eg, for findings concerning for more advanced tumors or with concern for violation of the gallbladder with bile spillage).

Calcification of the gallbladder is an uncommon condition related to chronic cholecystitis. The term “porcelain gallbladder” typically refers to the end-stage of the process with diffuse calcification of the gallbladder wall, often detected on plain abdominal x-rays, resulting in a brittle gallbladder with a bluish discoloration. Older series reported extremely high rates of malignancy associated with gallbladder calcification, and thus cholecystectomy was advocated. Modern series, however, report a much lower incidence of gallbladder carcinoma, and thus routine cholecystectomy has fallen out of favor. The pattern of calcification may be important in determining the risk of malignancy, as patients with selective mucosal calcification or incomplete calcification of the gallbladder wall appear to be at higher risk than those with complete gallbladder wall calcification. Thus, it is reasonable to reserve routine cholecystectomy for symptomatic patients and those with incomplete calcification. As cholecystectomy is a low-risk procedure and even minimal risk of harboring an aggressive malignancy may be unacceptable, surgery can also be
considered in low surgical risk patients with asymptomatic complete
gallbladder calcification.

STAGES 0 AND I (TIS-T1, N0, M0)

For Tis (carcinoma in situ) and T1a (cancer that invades the lamina propria
but does not extend into the muscularis) lesions, the available retrospective
data suggest that simple cholecystectomy is sufficient therapy in most cases,
with a cure rate approaching 100%. These lesions are most frequently
detected on pathological examination of gallbladders removed for presumed
benign disease. Patients diagnosed with gallbladder cancer in this manner
should undergo formal imaging-based staging, and the cholecystectomy
specimen should be carefully examined to ensure that all margins are
negative for cancer. Patients with imaging studies that reveal no evidence of
residual or metastatic gallbladder cancer and are found to have a cystic duct
margin that is positive for cancer should undergo reexploration with resection
to a negative margin, which may involve common duct excision and
hepaticojunostomy. In contrast, patients with negative margins and negative
imaging studies who undergo no additional treatment for their gallbladder
cancer have excellent outcomes that are unlikely to be improved by radical
surgery.\textsuperscript{28}

The management of T1b (cancer that invades the muscularis but does not
extend into the perimuscular connective tissues) lesions has been
controversial. In published series, the 5-year survival rate for patients with
T1b gallbladder cancer having undergone radical resection averages 87.5%,
whereas it averages only 61.3% in patients having undergone simple
cholecystectomy alone.\textsuperscript{29} Further, a recently published decision analysis
suggests that radical surgery (described later for stage II cancers) is
associated with improved survival compared to that associated with simple
cholecystectomy alone in most patients with T1b gallbladder cancer.\textsuperscript{29}
Therefore, we treat patients with T1b gallbladder cancer in the same way we
treat patients with T2 gallbladder cancer.

STAGE II (T2, N0, M0)

Patients found to have a T2 (cancer invasion into the perimuscular connective
tissues of the gallbladder) lesion in their cholecystectomy specimen following
surgery for presumed benign disease should undergo staging (as described earlier), and in the absence of contraindications, radical resection. Simple cholecystectomy is performed using a subserosal dissection plane, as the serosa of the gallbladder is continuous with Glisson’s capsule of the liver and thus there is no serosa between the gallbladder and the gallbladder fossa of the liver. Hence simple cholecystectomy may leave positive margins in the gallbladder fossa. Indeed, reexploration reveals residual tumor in 40% to 76% of these cases. In addition, the probability of regional lymph node metastasis in patients with T2 gallbladder cancer has been reported to range from 28% to 63%. These findings provide rationale for performing reexploration with liver resection and portal lymphadenectomy. There is convincing, albeit retrospective, evidence that such radical surgery is associated with improved survival for patients with T2 gallbladder cancer.

**STAGE III (T3, N0-1, M0 OR T1-3, N1, M0)**

A role for aggressive surgical resection for some stage III gallbladder cancers has been receiving increasing recognition. This stage includes T3 lesions (locally advanced cancers that perforate the gallbladder serosa or directly invade the liver and/or one adjacent organ) and T1 to T3 lesions associated with regional lymph node metastasis. Some have advocated neoadjuvant chemotherapy or neoadjuvant chemoradiation for this group of patients in order evaluate the biology of disease and better select patient for surgery.

Surgery for patients with T3 lesions requires careful planning and must be tailored to individual patients. For some patients with liver invasion, hepatic resections encompassing segments 4b and 5 may be sufficient. However, because the gallbladder fossa bridges both right and left hemilivers, and due to the proximity of the cystic plate to the inflow of the right liver, extended right hepatectomy is often required. Adjacent involved structures, such as the hepatic flexure of the colon, should be resected en bloc. Long-term survival rates ranging from 15% to 63% have been reported from some centers to be associated with these extended procedures for T3 lesions.

While the outcome for patients with lymph node metastases in the porta hepatis (N1) is considerably worse than for patients without uninvolved nodes (N0), the surgical approach is generally the same. The only possible exception would be the exceedingly unusual circumstance where a patient
with a T1a tumor is diagnosed with N1 disease in the absence of distant metastases. In such a scenario regional lymphadenectomy would be required.

**STAGE IV (T4 OR N2 OR M1)**

Stage IVA (invasion of the main portal vein, hepatic artery, multiple extrahepatic organs) and stage IVB (N2 and/or distant metastasis) disease is generally considered unresectable. Reports of radical procedures involving resection of the main portal vein and/or common hepatic artery exist, but these procedures are associated with increased morbidity and mortality rates without any proven survival benefit. The outcome of patients with multiple regional lymph nodal metastases (N2 disease) is similar to patients with M1 disease, and these patients are not thought to benefit from resection.

There is no evidence that debulking cholecystectomy provides any therapeutic or palliative benefit.

**Surgical Technique**

The surgical approach depends both on the stage of disease (as outlined above) as well as the clinical presentation. There are three common scenarios in which gallbladder cancer is discovered: (1) it can be found on pathologic review of a cholecystectomy performed for presumed benign disease; (2) it can be suspected or diagnosed preoperatively, either resulting from a workup for symptoms attributable to the tumor or found incidentally; or (3) it can be discovered intraoperatively, often on exploration for presumed cholecystitis. Specific considerations for each clinical scenario will be discussed separately.

**GALLBLADDER CANCER DIAGNOSED AFTER CHOLECYSTECTOMY**

When gallbladder cancer is diagnosed after a previous cholecystectomy, the pathology report, the operative report, and any imaging obtained prior to the cholecystectomy should be thoroughly reviewed. In addition to depth of penetration and margin status, particularly that of the cystic duct, the pathology report can provide information on tumor location. Similarly, pre-cholecystectomy imaging can provide information on tumor location as well as possible liver or nodal involvement. Knowing the tumor location (ie, neck,
body, or fundus; abutting liver, or on the side of gallbladder away from liver) may help in operative planning and in the interpretation of the operative findings on reexploration. After completing the staging evaluation as above, patients with T1b-T3 tumors are prepared for reoperation. Given the propensity of gallbladder cancer to seed wound sites, reexcision of all surgical wounds, including laparoscopic port sites, has been recommended. However, port site metastasis is usually associated with other peritoneal metastases and excision of port sites has not been proven beneficial.  

The operative report from the prior cholecystectomy and/or discussion with the surgeon can elicit findings suggestive of disseminated disease within the abdomen. In the absence of such findings, a diagnostic laparoscopy is unlikely to be beneficial in this setting.

We generally use an extended right subcostal incision that starts in the upper midline below the xiphoid and curves to a form a line subcostally on the right side that can extend as far as a point midway between the inferior costal margin and anterior superior iliac spine if necessary. We first conduct a thorough examination for metastases. Often, hilar and celiac lymph nodes can be palpated before opening the entirety of the incision. The liver and peritoneal surfaces are also inspected.

The scope of the operation then performed is similar to that described by Glenn and Hays in the 1950s, which entailed resection of the gallbladder fossa of the liver as well as a regional lymphadenectomy of the hepatoduodenal ligament (Fig. 65-3). We typically will perform the lymphadenectomy first. The hilar lymph node dissection proceeds similarly to that described below for perihilar cholangiocarcinoma, with the notable exception being that the bile duct is not routinely resected and is instead skeletonized along with the portal vein and hepatic artery. Some authors have advocated division of the bile duct, particularly as this facilitates the nodal dissection. While it is true that this makes the lymphadenectomy easier, it is associated with greater morbidity without improving nodal yield or survival. As with perihilar carcinoma, on performing the Kocher maneuver and initiating the hilar dissection, retropancreatic, celiac, periaortic, and pericaval lymph nodes can be inspected and palpated. Hard or enlarged nodes are sampled and subjected to frozen-section analysis. If these lymph nodes are positive for metastases, M1 disease is present and radical resection is aborted.
In the reoperative setting it is not uncommon for fibrosis to be encountered in the porta hepatis. It may be difficult to differentiate fibrosis from tumor. Information gleaned from review of the pathology report and the pre-cholecystectomy imaging (eg, tumor location and cystic duct margin status) may aid in this assessment. If invasion of the common duct is suspected, the extrahepatic biliary system can be resected from the superior border of the duodenum to just below the bifurcation. Common duct resection may also facilitate resection of bulky nodal disease in the hepatoduodenal ligament. The CBD is clamped and transected at the superior border of the duodenum. Similarly, the common hepatic duct is transected near its bifurcation. We take care to minimize spillage of bile that may contain cancer cells. The distal bile duct is oversewn with a slowly absorbable monofilament suture such as polydioxanone (PDS). The proximal bile duct is reconstructed with a Roux-en-Y hepaticojejunostomy as described below. If invasion of the right inflow (right portal vein or right hepatic artery) is found, an extended right
The basic conduct of a liver resection is discussed elsewhere; however, some points bear mentioning. Intraoperative US is usually performed and may help in providing information on the intrahepatic vascular anatomy as well as occult metastatic disease. The segmental portal pedicles are usually controlled within the liver parenchyma. As the middle hepatic vein is located directly anterior to the gallbladder fossa, separating segments 4b and 5, care must be taken to avoid bleeding from the vein and its branches. The base of the gallbladder fossa is in close proximity to the porta hepatis, and precaution should be given at the end of the liver resection when these structures are approached. In particular, injury to the right anterior portal pedicle and the portal pedicle of segment 8 within the liver should be avoided. The routine use of more extended liver resections has not been proven to be of benefit.40

GALLBLADDER CANCER SUSPECTED OR DIAGNOSED PREOPERATIVELY

For patients suspected of having resectable gallbladder cancer, the approach is similar. In this setting, we begin surgical exploration with laparoscopy, as even with a complete radiologic staging workup disseminated disease is occasionally found, and in these cases laparotomy can be spared.43 The degree of suspicion for gallbladder cancer beyond T1a must be determined preoperatively. The approach for polypoid lesions, which generally do not harbor malignancy, is described above. For masses with features concerning for malignancy, we do not perform laparoscopic cholecystectomy because of the risk for gallbladder perforation and tumor spillage. In these cases extended cholecystectomy is usually performed as the initial procedure. In some cases, frozen-section analysis may be used either prior to performing the extended cholecystectomy or after an extended cholecystectomy but prior
to the lymphadenectomy. Although determining depth of cancer invasion can be difficult on frozen sections, these grossly apparent cancers are likely to be at least T1b. For masses with invasion beyond the gallbladder, intraoperative diagnosis is not needed. It should be noted, however, that rarely benign conditions, in particular xanthogranulomatous cholecystitis, can mimic this condition. In the case of suspected resectable gallbladder cancer with invasion beyond the gallbladder (T3 tumors), extended liver resections and/or en bloc resection of adjacent organs may be required. Gallbladder cancers presenting with obstructive jaundice due to involvement of the bile duct are typically very advanced tumors. A resection with curative intent can rarely be performed and even when performed, long-term survival is rare.\(^4^4\)

**GALLBLADDER CANCER DIAGNOSED INTRAOPERATIVELY**

In cases where gallbladder cancer is diagnosed intraoperatively but was not suspected preoperatively, a thorough inspection of the liver and peritoneum for metastatic disease should be performed. If cancer is discovered during an open procedure, the porta hepatis and celiac origin should be palpated for nodal involvement. If extensive dissection has not begun, it is appropriate to close the patient and complete the radiologic staging exam. Similarly, if the gallbladder has been completely resected and frozen section reveals cancer, it is likely wise to terminate the operation so as to complete staging and consent the patient prior to performing radical resection. In some cases, gallbladder cancer may be discovered late in the procedure when difficulty is encountered in attempting to remove the gallbladder from the gallbladder fossa of the liver. In this circumstance, if expertise is available, it may be appropriate to perform an extended cholecystectomy and proceed to lymphadenectomy if frozen section confirms gallbladder cancer.

**Adjuvant Therapies**

Adjuvant chemoradiotherapy is commonly administered after resection of gallbladder cancers. External beam or intraoperative radiation therapy alone or in combination with 5-flourouracil (5-FU) has been associated with diminished rates of local recurrence. Recently results, of the phase III multicenter **BILCAP trial** from the United Kingdom, were reported in
abstract form. This trial randomized 447 patients with gallbladder (18%) and biliary cancer (19% intrahepatic, 28% perihilar, 35% distal) to capecitabine or observation following complete surgical resection. Although in the intention to treat analysis, the benefit in median overall survival for capecitabine did not reach significance (51 months versus 36 months, p = 0.097), the result was significant in the per protocol analysis (53 months versus 36 months, p = 0.028). Subgroup analysis from an older phase III trial randomizing 508 patients with pancreaticobiliary cancer (28% gallbladder cancer and 27% cholangiocarcinoma) to adjuvant treatment with fluorouracil and mitomycin C or observation showed improved survival with adjuvant treatment for patients with gallbladder cancer but not cholangiocarcinoma.

**Treatment of Unresectable or Metastatic Disease**

Of the several approaches that have been applied in patients with advanced gallbladder cancer, the only regimen supported by level one evidence is the combination of gemcitabine plus cisplatin. Data from a multicenter randomized controlled trial (Advanced Biliary Cancer (ABC)-02 trial) published in 2010 of patients with locally advanced or metastatic biliary tract cancer (of whom ~36% had gallbladder cancer) demonstrated that the combination of gemcitabine plus cisplatin is associated with improved overall and progression-free survival compared to gemcitabine alone. As such, this gemcitabine-cisplatin combination represents the current standard treatment option for patients with advanced biliary tract cancers, including gallbladder cancer. It should also be noted that based on the impressive results found for colorectal cancer with defective mismatch repair, patients with other solid tumors harboring defective mismatch repair were examined for response to the anti–PD-1 antibody pembrolizumab. In a series of 86 patients, including 4 with cholangiocarcinoma, responses were seen regardless of the cancers’ tissue of origin. Pembrolizumab is now approved for the treatment of patients with all metastatic and unresectable solid tumors having defective mismatch repair who have progressed through prior therapy and for whom there are no satisfactory treatment alternatives. Palliation of biliary obstruction, which can be required for advanced gallbladder cancer (Figs 65-4 and 65-5), is discussed below.
FIGURE 65-4  CT scan of advanced gallbladder cancer. The image demonstrates an advanced gallbladder cancer with extensive liver invasion. A stent has been placed for palliation of obstructive jaundice.
FIGURE 65-5 Palliation of gallbladder cancer. This radiograph depicts a Wallstent that has been placed for palliation of obstructive jaundice in a patient with advanced gallbladder cancer.

Outcomes

Data derived from the National Cancer Database support the nihilistic view traditionally associated with gallbladder cancer. In these population-based data, 5-year survival rates for patients with T1N0, T2N0, and T3N0 (or node-positive) disease are 39%, 15%, and 5%, respectively.

However, contemporary surgical series suggest that substantially improved outcomes can be achieved by the application of surgical resection of gallbladder cancers. In these reports, 5-year survival rates following
resection of T1 lesions range from 85% to 100%. With radical resection of T2, T3, and T4 lesions, reported 5-year postoperative survival rates range from 41% to 90%, 15% to 63%, and 2% to 25%, respectively. Radical resection of node-positive disease has been reported to be associated with 5-year survival in as high as 60% of patients, although some reported series contained no patients who survived 2 or more years among those with lymph node metastasis.\textsuperscript{30–37}

Reported morbidity and mortality rates associated with resection of gallbladder cancers range from 5% to 54% and from 0% to 21%, respectively. In general, the highest morbidity and mortality rates are associated with series describing more extensive resections.

The best reported outcomes among patients with unresectable biliary tract cancers are those from the ABC-02 trial. The median overall survival among patients treated with the combination of gemcitabine and cisplatin was 11.7 months, whereas it was 8.1 months in those treated with gemcitabine alone.\textsuperscript{47}

**CHOLANGIOCARCINOMA**

**Epidemiology**

In this discussion, the term *cholangiocarcinoma* is used to denote cancers with cholangiocyte (ie, biliary) differentiation arising in the liver or biliary tree, exclusive of the ampulla of Vater and gallbladder. Cholangiocarcinomas are classified into three groups according to their anatomical location: (1) intrahepatic (iCCA, 10% of cases), (2) perihilar (pCCA, 50% of cases), and (3) distal (dCCA, 40% of cases). pCCA is defined as lesions proximal to the cystic duct up to and including lesions involving the second-degree bile ducts. Bile duct tumors involving the hepatic duct bifurcation have historically been known as *Klatskin tumors.* This classification is helpful in terms of the differing clinical presentation and management for these three tumors, and there is now increasing consensus that these are three distinct entities in terms of epidemiology and pathobiology.

Approximately 6000 new cases of cholangiocarcinoma are diagnosed annually in the United States.\textsuperscript{1} Most patients are diagnosed in the fifth through the seventh decades of life. Unlike gallbladder cancer, for which
there is a clear female predominance, the incidence of bile duct cancer is slightly higher in males than in females.

Although most patients diagnosed with cholangiocarcinoma have no identifiable predisposing factors, several conditions clearly increase the risk of developing this cancer (Table 65-3). In Western countries, PSC is the most important risk factor; indeed, approximately 30% of cases of cholangiocarcinoma in the West are diagnosed in patients with PSC. Among patients with PSC, the estimated lifetime incidence of cholangiocarcinoma ranges from 5% to 10%, with approximately 50% of these cases being diagnosed within 24 months of the diagnosis of PSC. In addition, cholangiocarcinoma tends to be diagnosed at an earlier age (mean age in fourth decade of life) in patients with PSC than in the general population (mean age in seventh decade).23,50

<table>
<thead>
<tr>
<th>TABLE 65-3: RISK FACTORS FOR BILE DUCT CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Liver flukes infestation (<em>Opisthorchis viverrini</em> and <em>Clonorchis sinensis</em>)</td>
</tr>
<tr>
<td>Choledochal cysts</td>
</tr>
<tr>
<td>Caroli disease</td>
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<tr>
<td>Hepatolithiasis</td>
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<tr>
<td>Chemicals (eg, Thorotrast and dioxin)</td>
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<tr>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Lynch syndrome II</td>
</tr>
<tr>
<td>Bile duct adenoma and multiple biliary papillomatosis</td>
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</tbody>
</table>

In Asian countries, infestation with the liver flukes *Opisthorchis viverrini* or *Clonorchis sinensis* and hepatolithiasis are important risk factors for cholangiocarcinoma. Cirrhosis and hepatitis B or C viral infection have recently been recognized as important etiologic factors, especially for intrahepatic cases. Other risk factors include choledochal cysts, Caroli disease, and exposure to the radiological contrast agent Thorotrast. The management of choledochal cysts in terms of prevention of cholangiocarcinoma is discussed elsewhere in this book. Increased risk has been reported for workers in the auto, rubber, chemical, and wood-finishing
industries. Two genetic conditions (Lynch syndrome II and multiple biliary papillomatosis) have been identified as increasing the risk of developing bile duct cancer. Obesity and metabolic syndrome are reported as risk factors, particularly for intrahepatic cholangiocarcinoma.

**Pathogenesis and Pathology**

While there are several similarities in the pathogenesis and pathology of iCCA, pCCA, and dCCA, there are also notable differences. Recent genetic analyses have illustrated some of these distinctions. iCCA appears most dissimilar as compared to pCCA and dCCA. Genetic analyses comparing iCCAs to the other two types show that ERBB2/HER2 is less frequently altered in iCCAs, whereas genes of the FGF pathway are more frequently altered. SMAD4 may also be less frequently altered in iCCA. Alterations in K-ras, p53 and P16INK4A are prevalent in all cholangiocarcinomas. Alterations in chromatin remodeling genes such as ARID1A is common in iCCA and likely the other two types as well. Perhaps the most notable genetic difference between iCCAs and the other types involves mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2), which occur in approximately 20% of iCCAs and are generally not found in other types of cholangiocarcinomas. The pattern of mutations in cholangiocarcinomas associated with liver flukes also appears different from sporadic tumors.

Even the cell of origin may differ between iCCAs and the other types of cholangiocarcinoma. While it was previously suspected that all cholangiocarcinomas result from the transformation of cells of bile duct epithelium (cholangiocytes), it has recently been shown that this may not always be the case for iCCA. Liver cells (hepatocytes, hepatoblasts, and hepatic progenitor cells) can give rise to iCCA. A common cell of origin for iCCA and hepatocellular carcinoma (HCC) may explain the fact that many of the same etiologic factors are shared between these tumors and may also justify the fact that these tumors are often treated similarly. Further supporting the contention that iCCAs can originate from liver progenitor cells, it was recently shown that mutant IDH1/2 blocks liver progenitor cells from undergoing hepatocyte differentiation and promotes biliary differentiation and transformation to iCCA.

Greater than 90% of cholangiocarcinomas are adenocarcinomas. Other
cancer types include squamous cell carcinoma, small cell carcinoma, and sarcomas.

**Clinical Presentation and Diagnosis**

iCCAs can present with nonspecific symptoms, such as abdominal pain, anorexia, weight loss, and malaise. Another mode of presentation for these cancers is the detection of an asymptomatic intrahepatic mass on imaging studies. The most common presentation of pCCA and dCCA (~90%) is painless jaundice. Other manifestations of biliary obstruction, such as acholic stools, dark urine, and pruritis, are also prevalent. It should be noted that in cases of pCCA without the obstruction of biliary flow from all segments of the liver, jaundice may not be present. Even a small, well-vascularized portion of the liver can maintain a normal bilirubin, especially with the resultant atrophy of the obstructed portions of the liver and consequent hypertrophy of the drained portions. Jaundice can also be intermittent in the case of papillary tumors intermittently obstructing the bile duct through a ball valve mechanism. Abdominal pain, fatigue, malaise, and weight loss can occur with advanced disease. Signs of advanced cholangiocarcinomas include right upper quadrant abdominal tenderness, hepatomegaly (more likely with iCCA), and a palpable gallbladder (pCCA and dCCA). Cholangitis is unusual in the absence of prior biliary tract instrumentation.

The differential diagnosis for iCCA (liver mass) is usually HCC and metastatic tumors. The differential diagnosis for pCCA and dCCA includes benign biliary strictures due to conditions such as PSC, choledocholithiasis, Mirizzi syndrome, and postoperative strictures. For strictures of the mid-bile duct, gallbladder cancer must be considered, as cholangiocarcinomas arising at the level of the cystic duct insertion are uncommon. For dCCA, often the distinction between this tumor and other periampullary (ampullary, pancreatic, and duodenal) neoplasms may be unclear preoperatively.

In patients with iCCA or pCCA incompletely obstructing bile flow, laboratory studies may reveal an increased alkaline phosphatase level in the setting of normal bilirubin levels. In patients with pCCA and dCCA, laboratory tests are usually consistent with the presence of obstructive jaundice. Tumor markers (eg, CEA, CA 19-9, and CEA in combination with CA 19-9) may have utility in surveillance of patients with PSC and may be helpful in following the course of disease; however, their sensitivities and
specificities are too low for them to be applicable to screening or diagnosis in the general population. Elevated serum immunoglobulin G4 (IgG4) has been advocated to assess for lymphoplasmacytic sclerosing cholangitis, also known as IgG4-related cholangiopathy, an important mimic of malignant bile duct stricture; however, IgG4 can also be elevated, sometimes quite markedly, in cholangiocarcinoma.\textsuperscript{59}

Transabdominal US is a useful first study for evaluating obstructive jaundice. It can reveal dilation of the biliary tree. As the source of obstruction should be distal to biliary dilation, the location of the dilation (ie, confined to a portion of the liver, intrahepatic but not extrahepatic, or intrahepatic and extrahepatic) may help focus investigation on the location of the obstruction. Biliary dilation in the absence of a benign etiology such as choledocholithiasis suggests a possible biliary or, in the case of a distal obstruction, periampullary malignancy. Transabdominal US can also detect a liver mass incidentally or when used for screening in patient at risk for primary liver cancer (eg, cirrhotics and patients with chronic hepatitis B or C). US findings suspicious for cholangiocarcinoma typically require contrast-enhanced cross-sectional imaging (CT or MRI) for better characterization and surgical planning.

For iCCA, CT and MRI can both identify a mass and assess for vascular invasion. They may also identify other liver lesions, portal lymphadenopathy, and evidence of distant metastasis. iCCAs typically appear as a hypodense hepatic mass on unenhanced images with the development of peripheral rim enhancement in the arterial phase and progressive hyperattenuation on venous and delayed phases (\textbf{Fig 65-6}). MRI typically also shows the mass to be T2 hyperintense. MRI is not routinely preferred over CT but may provide improved detection and characterization of liver masses in patients with underlying cirrhosis.
FIGURE 65-6 CT scan of intrahepatic cholangiocarcinoma. The image shows a hyperattenuating lesion in Segment 4 of the liver.

For pCCA and dCCA, CT and MRI can identify the level of biliary obstruction, vascular involvement, and hepatic atrophy. In pCCA, there are typically dilated intrahepatic bile ducts, which can be unilateral or bilateral depending on the site of obstruction with a normal or collapsed gallbladder (unless the obstruction occludes the cystic duct) and a normal-caliber distal CBD. In dCCA, the entire intra- and extrahepatic biliary tree and the gallbladder are dilated. The presence or absence of a mass in the head of the pancreas may help in the differentiation from pancreas cancer. In addition to offering information on the site of the primary lesion, CT and MRI offer valuable information necessary for staging and planning of therapies, including the presence or absence of local vascular invasion, regional lymphadenopathy, distant metastasis, and liver atrophy. Longstanding unilateral bile duct obstruction typically results in atrophy of the affected hemiliver together with hypertrophy of the unaffected hemiliver (atrophy-hypertrophy complex). Absence of the atrophy-hypertrophy complex can suggest vascular encasement by tumor. MRI is not routinely indicated over CT but may provide greater sensitivity in detection of masses associated with pCCA and dCCA and provides more precise delineation of the biliary anatomy.
More invasive studies are sometimes required in the preoperative evaluation of patients with cholangiocarcinoma. For iCCA, since a metastatic tumor to the liver often can have the same appearance and cannot even be excluded by a biopsy showing adenocarcinoma, upper endoscopy and colonoscopy can be considered to diagnose an occult primary gastrointestinal tumor. The cross-sectional imaging should also be examined closely for other tumors, such as pancreas cancer. For dCCA, upper endoscopy can help exclude another source of biliary obstruction such as duodenal or ampullary tumors.

Direct cholangiography is not routinely indicated preoperatively; however, many patients will have had endoscopic retrograde cholangiopancreatography (ERCP) and/or percutaneous transhepatic cholangiography (PTC) prior to referral. It should be noted that in many centers, particularly in Japan, detailed cholangiography is viewed as an essential part of preoperative planning for pCCA (Fig. 65-8, left). This practice is not widely shared in the United States. Direct cholangiography is utilized when biliary drainage or a histologic diagnosis is desired. As some reports suggest that MRCP when applied to patients with cholangiocarcinoma offers information equivalent to that offered by CT scanning and direct cholangiography combined (Fig. 65-8, right), MRCP has been supplanting traditional cholangiography in the evaluation of patients with suspected cholangiocarcinoma in many centers. Unlike direct cholangiography, MRCP is noninvasive and does not require instrumentation or the injection of contrast material in the biliary ductal system. This may be particularly important in pCCA when resection cannot be accomplished (see discussion of palliation for malignant biliary obstruction below).

FIGURE 65-8 Percutaneous transhepatic cholangiography (PTC) and magnetic resonance cholangiography (MRCP) of hilar cholangiocarcinoma. The images depict a stricture at the confluence of the hepatic ducts in a
patient with a Klatskin tumor. In the left image, the biliary system is accessed through the right liver with lack of opacification of the common hepatic duct or the left biliary system. A stent had been placed by ERCP, but it failed to cross the stricture. In the right images, the MRCP shows the same stricture as seen by dilation of both the right and left intrahepatic biliary ducts with a non-dilated extrahepatic biliary system along with lack of visualization of the biliary confluence.

Similar to gallbladder cancer, PET scanning for the staging of cholangiocarcinoma is not universally accepted; however, some studies show that it can identify occult metastases to regional lymph nodes and distant sites. PET is most useful in the evaluation of indeterminate findings on cross-sectional imaging.

If surgical exploration is planned, a preoperative attempt at histologic diagnosis is not indicated. This is particularly true with pCCA and dCCA, where obtaining a tissue diagnosis is notoriously difficult. Brushings obtained by ERCP or PTC are only 15% to 68% sensitive. A mass is not often detected on cross-sectional imaging precluding percutaneous fine needle aspiration (FNA). EUS-FNA may have improved sensitivity (approaching 80%) compared to brushings, and is feasible in proximal as well as distal tumors. It should also be noted that for patients with pCCA in whom transplantation is considered, due to the possibility of seeding and the need for immunosuppression, a transperitoneal biopsy attempt is considered an exclusion criterion. It bears mentioning that while resection of presumed malignant hilar or distal bile duct obstruction without a preoperative diagnosis of cancer will occasionally yield a benign diagnosis, the rate of such occurrences is low (~10%).

A particularly challenging situation can arise in patients with PSC, 20% to 50% of whom will develop a benign dominant biliary stricture. These dominant strictures can be morphologically indistinguishable from cholangiocarcinomas on cholangiography. Cytological examination of brushings obtained during ERCP is the most common modality used for the diagnosis of cholangiocarcinoma in this setting; however, as in patients without PSC, the sensitivity of this modality (40%-80%) is poor. EUS-FNA, which is the most accurate modality for making a diagnosis of cholangiocarcinoma, should be applied in patients with equivocal or negative brush cytological findings if clinical suspicion of cholangiocarcinoma in a
Morphological Classification, Anatomic Classification, and Staging

iCCAs are typically classified as mass-forming, periductal infiltrating, and intraductal based on their morphological pattern of growth. The mass-forming type accounts for almost 90% of cases. pCCAs and dCCAs are morphologically classified as sclerosing, nodular, or papillary (analogous to the classification scheme for gallbladder adenocarcinomas). Sclerosing (scirrhus) tumors, which comprise over 80% of cholangiocarcinomas, are associated with an intense desmoplastic reaction, tend to be highly invasive, and are associated with low resectability rates. Nodular tumors have the appearance of constricting annular lesions and are also associated with low resectability rates. Often tumors have both nodular and sclerosing features, and thus the term nodular-sclerosing is often used. Papillary tumors are rare (~10% of cases) and present as bulky masses that project into the bile duct lumen. It should be noted that although these tumors tend to spread within the bile duct lumen suggesting diffuse involvement, they often arise from a single well-defined stalk, facilitating resection. Because these lesions tend to cause symptomatic obstructive jaundice relatively early in their progression and because they are typically contained completely within the bile duct, they are associated with higher resectability rates than sclerosing or nodular tumors. Papillary tumors are associated with a more favorable prognosis, and the same may be true of the intraductal type for iCCAs.

The AJCC staging system now contains separate staging systems for iCCA (Table 65-4), pCCA (Table 65-5), and dCCA (Table 65-6). For iCCA, AJCC staging is based on the major prognostic factors: number of tumors, tumor size, vascular invasion, lymph node metastasis, and distant metastasis. For pCCA, the T stage for the AJCC system incorporates both depth of invasion and extent of tumor involvement as a surrogate for resectability (see discussion of Memorial Sloan-Kettering Cancer Center [MSKCC] anatomical classification below). Similarly for dCCA, the T stage incorporates depth of invasion (now measured in mm in the AJCC eighth edition), with T4 tumors representing tumors that are unresectable due to major vascular invasion. AJCC staging for pCCA and dCCA also accounts
for metastasis to regional lymph node and distant sites.

### TABLE 65-4: TNM STAGING OF INTRAHEPATIC BILE DUCT CANCER

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IIIIB</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Tis, carcinoma in situ; T1, solitary tumor without vascular invasion; T1a, solitary tumor ≤5 cm without vascular invasion; T1b, solitary tumor >5 cm without vascular invasion; T2, solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion; T3, tumor perforating visceral peritoneum; T4, tumor involving local extrahepatic structures by direct invasion; N0, no regional lymph node metastasis; N1, regional lymph node metastasis present (for right liver [segments 5–8] regional lymph nodes include hilar, periduodenal, and peripancreatic lymph nodes; for left liver [segments 2–4] -regional lymph nodes include inferior phrenic, hilar and gastrohepatic lymph nodes); M0, no distant metastasis; M1, distant metastasis present (metastasis to celiac and/or periaortie and pericaval lymph nodes is considered distant metastasis).


### TABLE 65-5: TNM STAGING OF PERIHILAR BILE DUCT CANCER
<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
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<tbody>
<tr>
<td>Stage I</td>
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<td>T2a-b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Tis, carcinoma in situ; T1, cancer confined to bile duct, with extension up to the muscle layer or fibrous tissue; T2, cancer invades beyond the wall of bile duct to surrounding adipose tissue, or cancer invades adjacent hepatic parenchyma; T2a, cancer invades beyond the wall of bile duct to surrounding adipose tissue; T2b, cancer invades adjacent hepatic parenchyma; T3, cancer invades unilateral branches of the portal vein or hepatic artery; T4, cancer invades main portal vein or its branches bilaterally, or the common hepatic artery, or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery invasion; N0, no regional lymph node metastasis; N1, metastasis to one to three regional lymph node metastasis (hilar, cystic duct, common bile duct, hepatic artery, posterior pancreaticoduodenal, and portal vein); N2, metastasis to four or more regional lymph nodes; M0, no distant metastasis; M1, distant metastasis.


**TABLE 65-6: TNM STAGING OF DISTAL BILE DUCT CANCER**
As surgical planning and assessment of resectability are important in the preoperative evaluation of pCCA, additional anatomical classification systems are widely used. The modified Bismuth-Corlette classification scheme stratifies tumors based on the extent of bile duct involvement (Fig. 65-7, top). This system may be useful for surgical planning but does not assess resectability. The MSKCC classification scheme, which takes into account extent of bile duct involvement as well as vascular invasion and hepatic atrophy, may help determine both the resectability for the tumor and the necessary surgical procedure (Fig. 65-7, bottom). Both the Bismuth-Corlette and the MSKCC systems, unlike the AJCC T stage for pCCA, are based on information that can be determined preoperatively from imaging studies and thus are of particular use to surgeons.
FIGURE 65-7  Bismuth-Corlette classification scheme and the MSKCC staging system for perihilar cholangiocarcinoma. In the Bismuth-Corlette system (top), Type I tumors are located distal to the biliary confluence, Type
II tumors involve the junction of the right and left hepatic ducts, Type III tumors involve the secondary biliary confluence on either the right or the left, and Type IV tumors involve the secondary biliary confluence on both sides. In the MSKCC system (bottom), T1 tumors involve the biliary confluence with or without unilateral extension to second order biliary radicles, T2 tumors also have ipsilateral portal vein involvement and/or ipsilateral hepatic atrophy (not shown), and T3 tumors have bilateral extension to second-order biliary radicles or unilateral extension to a second-order biliary radicle with contralateral portal vein involvement and/or contralateral hepatic atrophy (not shown).

**Surgical Therapy**

As is the case for gallbladder cancer, complete surgical extirpation is the only potentially curative therapy for patients with cholangiocarcinoma. Therefore, all fit patients suspected of having resectable cholangiocarcinoma should be offered surgery. Specific issues regarding preoperative treatment and choice of treatment modality are discussed below. Technical issues are then reviewed separately.

**ROLE OF PREOPERATIVE BILIARY DRAINAGE**

The utility of preoperative biliary stenting in patients with biliary obstruction from cholangiocarcinoma is controversial. Available retrospective data and one recently reported multicenter randomized controlled trial (DRainage vs OPeration [DROP] trial) suggest that among patients undergoing pancreaticoduodenectomy for periampullary cancers, routine preoperative biliary stenting is associated with increased perioperative morbidity rates, especially with respect to infectious complications. Therefore, we do not recommend routine preoperative stenting for patients with distal bile duct cancers. Instead, selective application of stenting in patients with obstructive jaundice who experience significant delay until surgery is performed (e.g., those undergoing neoadjuvant therapy) is appropriate. Furthermore, as patients with bilirubin >14.6 mg/dL were excluded from the DROP trial, and as profoundly elevated bilirubin can result in end organ dysfunction, the safest approach for these patients is not clear. This experience should not be extrapolated to patients with pCCAs, for whom the relationship between
preoperative stenting and operative outcomes is less clear. Some authors believe stents placed preoperatively make intraoperative assessment of tumor extent more difficult. However, as liver resection is indicated for most patients with pCCA (see below), there is concern about postoperative hepatic insufficiency due to the potentially impaired ability of the remnant liver to regenerate if biliary flow from that segment was obstructed preoperatively. Retrospective data indicate that preoperative biliary drainage may be of benefit prior to extended resections in patients expected to have a small future liver remnant (FLR), but that routine drainage may not be required.

When preoperative drainage is planned for patients with pCCA, a few points bear considering. First, as a potential benefit of drainage is the relief of obstruction in the portion of liver that will need to regenerate after resection, drainage of the FLR as opposed to the liver to be resected is preferred. The selection of what portion of the liver should be resected follows below. Second, it should be kept in mind that the patient may be found to be unresectable on exploration, so drainage should be planned according to the general principles for palliating hilar biliary obstruction discussed below. Notably, drains should be carefully placed without injecting contrast or instrumenting segments of the liver that are not drained, as cholangitis can subsequently develop in those segments. As discussed below, there is controversy over whether this can be effectively accomplished with ERCP as opposed to PTC; however, PTC has other disadvantages (eg, need for external drain, potential injury to liver). The ideal technique for preoperative biliary drainage is currently the subject of a randomized trial (DRAINAGE trial). Lastly, when drainage is accomplished via PTC, as biliary obstruction or diversion can be associated with malnutrition and impaired intestinal barrier function, attention should be given internal drainage or replacing bile into the intestine.

**ASSESSMENT OF RESECTABILITY FOR pCCA**

Resectabilty for pCCA depends on the ability to maintain a sufficient FLR after surgery. The general principles of liver resection are discussed elsewhere in this textbook, but are worth briefly reviewing here as it pertains to pCCA. After liver resection, the FLR needs to be of sufficient volume to be perfused by the portal vein and hepatic artery, to have outflow through a hepatic vein, and to have biliary drainage. As pCCAs are, by definition,
tumors in the hilus of the liver, while hepatic venous outflow is seldom a concern, maintaining an adequately sized remnant with portal venous and hepatic venous inflow as well as biliary drainage always needs to be considered. Thus, prohibitions to hepatic resection without vascular reconstruction include (1) bilateral invasion of portal vein and/or hepatic artery branches, (2) invasion of the main portal vein and/or hepatic artery, or (3) unilateral involvement of the hepatic vein and/or hepatic artery to the only side of the liver that could otherwise be preserved (ie, opposite side with non-reconstructable bile duct involvement or significant atrophy). Similarly, the side of the liver to be preserved (ie, with no significant atrophy, direct tumor involvement, or inflow issues) needs to be able to have the bile duct resected with a negative margin and reconstructed, thus (4) bilateral hepatic duct involvement to secondary radicles bilaterally and (5) unilateral duct involvement to the secondary radicles with contralateral vessel involvement and/or liver atrophy is considered unresectable. The MSKCC anatomical classification, which is mostly incorporated into the AJCC T stage for pCCA, well illustrates these principles of resectability. It should be noted that as with other major liver resections, in cases where an anticipated resection is expected to leave a small FLR, preoperative portal vein embolization (PVE) of the side of the liver to be resected to induce contralateral hypertrophy can be considered.

NEOADJUVANT CHEMORADIOOTHERAPY AND TRANSPLANTATION VERSUS RESECTION FOR pCCA

While surgical resection has long been considered the standard of care for fit patients with technically resectable disease, recently neoadjuvant chemoradiotherapy followed by orthotopic liver transplantation (OLT) has become a preferred approach for selected patients in some centers. Initial reports of OLT without neoadjuvant treatment (mainly for technically unresectable patients or patients with underlying liver disease) revealed 5-year survival rates averaging approximately 20% with some reports of long-term survivors, although many of these patients had small tumors discovered incidentally. The University of Nebraska and the Mayo Clinic established an intensive protocol of neoadjuvant treatment followed by OLT for carefully selected and staged patients, and by 2005 were reporting provocative initial results. The protocol consists of external beam radiation followed by
brachytherapy (transcatheter radiation) through catheters placed by ERCP or PTC along with radiosensitizing 5-fluorouracil, followed by chemotherapy (oral capecitabine) continued until the day of transplantation. After the initial radiochemotherapy, patients undergo a staging operation to assess the tumor extent and the presence of metastatic disease. At staging, lymph nodes are biopsied. Patients with nodal or distant metastases are excluded from OLT. By 2009, the United Network for Organ Sharing (UNOS) accepted pCCA as an indication for organ allocation. Subsequent studies have shown encouraging outcomes when this approach has been applied at other centers. There are important difficulties, however, in comparing these results to those obtained with resection. The patients who are offered neoadjuvant chemoradiotherapy followed by OLT are highly selected due to the intensity of this regimen and the stringent criteria applied to potential OLT candidates. Also, as evidence suggests that much of the benefit of this approach may be due to the neoadjuvant treatment rather than OLT, it remains to be seen whether similar results can be obtained with neoadjuvant therapy and surgical resection. Further clinical research in this area is needed. Currently, neoadjuvant radiochemotherapy should be strongly considered for patients with locally advanced pCCA not technically amenable to resection (eg, tumors involving second-order biliary radicles bilaterally) and in patients with underlying liver disease, such as PSC, where the results of resection have been less favorable.

Surgical Technique

Resectable iCCAs are treated using standard liver resections, and dCCAs are treated by pancreaticoduodenectomy. These procedures are discussed elsewhere in this textbook. A few points specific to these tumors, however, bear mentioning. First, as staging laparoscopy can identify peritoneal and liver metastases in a significant proportion of patients, its use should be considered for iCCA. In contrast, the yield of diagnostic laparoscopy for dCCA in patients staged with contemporary imaging is low. For iCCA, multifocal tumors generally represent metastatic disease, so this is usually a contraindication to resection. Acceptable results for resection of limited multifocal disease in selected patients have been reported. For iCCA, intraabdominal lymph nodes are the most common site of metastatic spread
and are present in up to 75% of patients. Lymph node involvement outside of hilar, periduodenal, and peripancreatic lymph nodes for right liver tumors and outside of inferior phrenic, hilar and gastrohepatic lymph nodes for left sided tumors is considered metastatic and is generally considered a contraindication to surgery. Even lymph node metastasis to the regional lymph nodes portends a poor prognosis, so all grossly enlarged lymph nodes should be sampled and resection considered only in selected cases. As occult regional lymph node metastases are common and represent an important prognostic factor, regional lymph node dissection (as below except with preservation of the bile duct) should be considered; however, it is unknown whether this provides any therapeutic benefit.

The remainder of the discussion focuses on our surgical approach to metastatic or resectable pCCA. Reports suggest that 25% to 30% of patients undergoing laparoscopic exploration for cholangiocarcinoma are found to have unresectable disease during laparoscopy, and thus we generally start the operation with a staging laparoscopy. If laparoscopic examination fails to reveal metastasis, we proceed with laparotomy through an extended right subcostal incision that starts in the upper midline below the xiphoid and curves to a form a line subcostally on the right side that can extend as far as a point midway between the inferior costal margin and anterior superior iliac spine if necessary. A small portion of the incision can first be opened to assess for celiac lymphadenopathy. The presence of metastasis in non-regional lymph nodes (periaortic, pericaval, superior mesenteric artery, and/or celiac artery) is a contraindication to radical resection, and thus during the early part of the exploration, special attention is given to assessment of these nodes. Enlarged lymph nodes are biopsied and subject to frozen section analysis.

The surgeon must be prepared to perform a liver resection, which is necessary in the vast majority of cases. Liver resection is usually required to obtain a margin-negative resection. Even without vascular involvement, hilar tumors spread longitudinally in or along the bile duct wall, and thus the ability to achieve a bile duct margin-negative resection is often compromised by dividing both the right and left bile ducts outside the liver. In the case of equal involvement of the right and left bile ducts extending proximally from the bifurcation, the extrahepatic portion of the left bile duct is typically longer, as this duct traverses the underside of segment 4 before entering the liver in the umbilical fissure. In this case, a right hepatectomy can usually
increase the distance from tumor to the bile duct margin, which would thus be just outside the left liver to be preserved. Furthermore, heptatectomy increases the chance for a circumferential margin-negative resection, as preservation of the entire liver requires dissecting the tumor off the hilar plate bilaterally and off the caudate posteriorly. It should be noted that again in the case of a tumor with equal distance from the liver along the right and left bile ducts, a right-sided resection may be preferred because the right hepatic artery crosses the bile duct (usually posteriorly) in close proximity to the bifurcation, and thus removing this structure en bloc with the specimen can also increase the chance for a negative circumferential margin. It may be possible to achieve margin-negative resections without heptatectomy for the unusual pCCAs that are completely distal to the bifurcation (Bismuth-Corlette type I), but it should be considered that overall, the best outcomes for resection of pCCA have been reported when liver resection is performed, and that the benefit of liver resection seems to be apparent even in the proportion of patients achieving a microscopically margin-negative resection.67,81,82

We next divide the ligamentum teres and take down the falciform ligament from the anterior surface of the liver. The liver is then inspected and palpated to assess for metastases. An US of the liver is performed both to assess for metastases and to confirm the intrahepatic vascular anatomy. We then open the lesser sac and perform a wide Kocher maneuver. The retropancreatic lymph nodes are thus assessed and the porta hepatitis exposed.

The sequence of following steps may vary based on the clinical scenario. Usually at this point, the bile duct is divided just proximal to the duodenum and reflected upward. The distal bile duct is then oversewn with a slowly absorbable monofilament suture such as PDS. In situations where it is suspected the tumor is likely to be unresectable, the surgeon may attempt to lower the hilar plate (see below) and perform some of the dissection of the bile duct from the vessels to make an assessment of resectability prior to dividing the bile duct. With the bile duct transected distally, the fatty tissue containing the lymph nodes is also divided at the level of the duodenum and reflected toward the liver along with the bile duct. The common bile duct and nodal tissue are dissected off the portal vein and hepatic artery extending superiorly (Fig. 65-9). The gallbladder and cystic duct are then taken down from the liver and the cystic artery is divided. The entire extrahepatic biliary
apparatus (common/hepatic bile duct, cystic duct and gallbladder) are then retracted toward the liver and dissection continued superiorly toward the liver, skeletonizing the vessels that will remain.

**FIGURE 65-9** Resection of hilar cholangiocarcinoma. This illustration shows the extrahepatic biliary tree along with the portal lymph nodes being dissected off of the portal vein and hepatic arteries. The dissection proceeds in a cephalad direction following transection of the distal bile duct.

At this point, the hilar plate is lowered by incising the liver capsule at the base of segment 4 and extending this incision between the gallbladder fossa and the umbilical fissure (Fig. 65-10). Dissection is continued between the biliary bifurcation and the liver separating the extrahepatic portions of the right and left ducts extending proximally from the bifurcation. The tumor can then be palpated in an attempt to assess its proximal and distal extent. During this portion of the dissection, a decision about which portion of the liver is to be resected must be made. The principles of such a determination are the same as in the preoperative assessment outlined above. It must be assured
that an adequate length of uninvolved extrahepatic bile duct exists on the side of the liver to remain in order to transect the bile duct with a sufficient margin from the tumor and preserving enough bile duct for reconstruction. Further dissection may be required at this point posterior to the biliary system to assure that the portal vein and hepatic artery to the FLR are free of the tumor.

**FIGURE 65-10** Lowering of hilar plate. The biliary confluence and portal lymphatic tissue are separated from their attachments to the liver capsule at the base of segment 4.

The bile duct on the side of the FLR as well as the portal vein and hepatic artery to the contralateral liver must then be divided (Fig. 65-11). The order in which this is accomplished may vary depending on the circumstance. Often by dividing the bile duct and reflecting the tumor along with the biliary system and nodal tissue toward the side of the liver to be resected, better exposure is obtained for division of the vessels, particularly the portal vein.
In some situations, the liver can be divided before dividing the bile duct, as splitting the liver facilitates circumferential exposure to the bile duct. Frozen sections of the bile duct are not routinely taken, as they can be falsely negative, and resection of a few extra millimeters of bile duct in the setting of an initial positive margin, even if a negative margin is ultimately achieved, appears to provide little if any benefit. Instead, every attempt is made to resect the bile duct as proximal as possible on the side of the liver to remain. Frozen sections of the margins should be checked in the setting of attempting resection of a pCCA without liver resection, as converting to a liver resection could provide ample additional margin from the tumor in the setting of a positive frozen section on one side.

**FIGURE 65-11** Division of the hepatic duct, portal vein, and hepatic artery. The bile duct on the side of the liver to be preserved (right hepatic duct in illustration) as well as the portal vein and hepatic artery on the side of the liver to be preserved (left portal vein and left hepatic artery in illustration) are divided.
Some authors believe that the caudate should be resected in all cases of pCCA, while others believe it can be retained selectively. The argument for routine caudate resection is that in order to preserve the caudate, the tissue between the caudate and the biliary bifurcation/portal hepatitis, including the caudate bile duct, must be divided, thus potentially leaving tumor along with the caudate. If the tumor extends proximally from the bifurcation into the left bile duct, the caudate should be routinely resected, as the caudate bile duct, which usually drains into the left bile duct, may also be involved. The caudate can be resected by first mobilizing the caudate posteriorly off the inferior vena cava (IVC), which entails division of all the caudate veins draining into the IVC, and dividing the attachments of the caudate to the main portal vein and hepatic artery as well as their branches to the FLR. (The main caudate inflow typically comes from the left side.) For a left hepatectomy with caudate resection, the caudate process (the portion of the caudate where it attaches to the right posterior sector of the liver) must be divided, along with the typical division between the right and left hemilivers, during parenchymal transection.

In order to prepare for liver resection, with the vessels and bile duct divided and the biliary/nodal tissue reflected toward the specimen side, a line of parenchymal dissection is then mapped out. The plane can begin in the principle plane of the liver between the right and left hemilivers; however, in the area of the porta hepatis it will stay close to where the bile duct, portal vein, and hepatic artery enter the FLR to achieve the maximal margin (Figs 65-12 and 65-14). The parenchymal dissection (and control of the hepatic vein[s]) do not substantially differ from that described elsewhere in this textbook.
FIGURE 65-12 Liver after resection of Klatskin tumor with left hepatectomy and caudate resection. The left panel shows an illustration depicting the appearance of the liver and portal structures after resection. The right panel shows an intraoperative photograph of the same. The sutures are placed through the right anterior and right posterior hepatic ducts on the surface of the remnant liver. The arrows mark where the left portal vein and left hepatic arteries were divided.

FIGURE 65-13 Resection of hilar cholangiocarcinoma. This illustration depicts the resection specimen following removal of the extrahepatic bile
duct en bloc with the left lobe of the liver.

FIGURE 65-14 Creation of the hepaticojejunostomy. The biliary–enteric anastomoses is performed using the method of Blumgart and Kelley with the anterior row of sutures used to splay open the bile duct while the posterior row of sutures is placed through the bile duct and jejunotomy.

While vascular reconstructions are sometimes used in the setting of vascular involvement during the resection of pCCA in appropriately selected patients, the description of these techniques are beyond the scope of this discussion. In rare cases, cholangiocarcinoma can involve the distal bile extending into the pancreas in addition to involving the biliary bifurcation. Combined liver resections with pancreaticoduodenectomies have been described, but these are morbid procedures.
Biliary reconstruction is accomplished between the remaining bile duct or ducts and a Roux-en-Y loop of jejunum using the technique of Blumgart and Kelley (Fig 65-13).\(^8^4\) We divide the jejunum just distal to the ligament of Treitz and take the distal divided end retrocolically toward the liver. A single-layer anastomosis is created using 4-0 slowly absorbable monofilament suture such as PDS. The anterior row of sutures is taken full thickness through the bile duct and hung over the retractor to splay open the bile duct. An appropriately sized jejunotomy is created and sutures are taken through the full thickness of both the bile duct and jejunum walls. The anterior row of sutures is then taken through the full thickness of the jejunum before tying and dividing all the sutures (Fig. 65-15). In the case where there is more than one duct to anastomosis (eg, right anterior and posterior sectoral ducts are separated), it is usually easier to approximate the multiple ducts together with sutures through the lateral walls and treat as one as opposed to creating separate anastomoses to the jejunal loop. Intestinal continuity is restored by creating a jejunojejunostomy between the proximal end of the divided jejunum and the Roux loop of jejunum 60 cm distal to the hepaticojejunostomy. We place a Jackson-Pratt drain posterior to the hepaticojejunostomy and attach the end to a bile bag.
**FIGURE 65-15** Completed reconstruction. This illustration depicts the appearance of the remnant liver with the biliary enteric anastomosis at the completion of the operation.

**Adjuvant Therapies**

Adjuvant chemotherapy, radiotherapy, or chemoradiotherapy is commonly offered, based on available data. However, unequivocal efficacy data derived
from prospective randomized clinical trials are lacking (see discussion in the section on adjuvant therapies for gallbladder cancer). Similarly, neoadjuvant therapy, associated with anecdotal reports of tumor response sufficient to permit margin-negative resection in patients with advanced cholangiocarcinoma, needs to be studied further.

**Treatment of Unresectable or Metastatic Disease**

Recently published results of the **ABC-02 trial** (discussed earlier in the section on treatment of unresectable or metastatic gallbladder cancer) indicate that the combination of gemcitabine plus cisplatin should be offered to patients with advanced bile duct cancer. While this trial also included gallbladder and ampullary cancers, nearly 60% of patients who were enrolled in this multicenter phase III trial had locally advanced or metastatic bile duct cancer. Administration of the gemcitabine-cisplatin combination was associated with prolongation of overall and progression-free survival compared to administration of gemcitabine alone. It should be noted that while the magnitude of benefit for this treatment did not appear to differ based on whether patients had iCCA, pCCA, dCCA, gallbladder cancer, or ampullary cancer in the subgroup analysis, in the group of patients with pCCA (and ampullary cancer) the benefit was not statistically significant. Checkpoint inhibitor therapy, specifically pembrolizumab, may be of benefit for metastatic or unresectable cholangiocarcinoma with defective mismatch repair (discussed earlier in the section on treatment of unresectable or metastatic gallbladder cancer).

While chemotherapy is the only treatment for metastatic and unresectable cholangiocarcinoma validated by level one evidence, liver-directed therapies are increasingly being used for liver-only iCCA. This approach is extrapolated from HCC and derives from the possible common origin of iCCA and HCC as well as increasing data reporting favorable results when applied to iCCA. Reports of transcatheter arterial chemoembolization, (TACE) transcatheter arterial radioembolization (TARE), and radiofrequency ablation (RFA) show that these treatments are safe and possibly efficacious. As in HCC, underlying liver disease may be the only limitation to surgical resection, making alternative locoregional therapies attractive.
Outcomes

Fewer than 50% of patients diagnosed with perihilar cholangiocarcinoma are able to undergo curative resection. Reported 5-year postoperative survival rates for patients with these cancers are highly variable in modern series; they range from approximately 10% to 50%.\textsuperscript{77,85} In general, the highest survival rates are associated with series containing a high proportion of cases in which R0 resection was achieved. Series containing the highest R0 resection rates (>75% of cases in some published experiences) tend to be reported by institutions where liver resection is applied liberally to patients with cholangiocarcinoma.\textsuperscript{77,85} A caveat to remember is that these same series also tend to be associated with the highest perioperative mortality rates (up to 14% in some cases).

For patients with intrahepatic cholangiocarcinoma, reported 3-year survival rates following curative resection with negative margins range from 22% to 66%. For patients with distal cholangiocarcinoma, 5-year survival rates following pancreaticoduodenectomy range from 15% to 25% in most reported series. Among patients with node-negative disease, 5-year postoperative survival rates as high as 54% have been reported.

The best reported outcomes among patients with unresectable biliary tract cancers are those from the ABC-02 trial. The median overall survival among patients treated with the combination of gemcitabine and cisplatin was 11.7 months, whereas it was 8.1 months in those treated with gemcitabine alone.\textsuperscript{47}

PALLIATION OF MALIGNANT BILE DUCT OBSTRUCTION

Patients with gallbladder cancer and cholangiocarcinoma are often faced with bile duct obstruction. Surgical resection in these cases relieves the bile duct obstruction. The role of preoperative stenting of the bile duct obstruction for resectable tumors is discussed above. The management of malignant bile duct obstruction in cases of metastatic, unresectable, or recurrent gallbladder cancer and cholangiocarcinoma deserves special mention. While relief of obstruction for patients with distal bile duct obstruction is relatively straightforward, palliation of perihilar obstructions is much more difficult. As cholangitis seldom occurs in the setting of malignant biliary obstruction prior
to instrumentation of the biliary system, intervention is rarely urgent or emergent. Instead, the role of biliary decompression and the most effective way to achieve it, if indicated, should be deliberately considered, ideally in a multidisciplinary setting.

The goal of biliary decompression must be carefully considered. Jaundice or dilated ducts on imaging themselves do not necessarily warrant intervention. Symptomatic relief or intractable pruritis or cholangitis do benefit from drainage. Administration of effective chemotherapy for patients with gallbladder cancer or cholangiocarcinoma is often contingent on biliary drainage for effective metabolism or excretion, so it is rational to relieve biliary obstruction in patients who elect to receive systemic treatment. It should be noted, however, that other than for relief of pruritis, biliary decompression was not shown to improve quality of life in a prospective trial. 86

Several interventions have been attempted for the relief of biliary obstruction. Of these, surgical bypasses and endoscopic or percutaneous stents or drains are the most common. While surgical bypasses have been shown to be more durable and associated with less need for reintervention as compared to endoscopic or percutaneous stents for both distal and perihilar obstructions, in practice, endoscopic or percutaneous biliary stenting are most often used preferentially due to the lower initial morbidity. Surgical biliary bypass is usually reserved for patients who are found to have unresectable disease at the time of surgical exploration or those in whom nonsurgical stenting cannot be accomplished.

The endoscopic approach to distal bile duct obstructions is generally preferred over the percutaneous approach. Endoscopic stenting is associated with low procedure-related morbidity and mortality and does not require an external drain. In contrast, the percutaneous transhepatic approach often requires at least temporary placement of an external drain. The choice of an endoscopic or percutaneous approach for drainage of perihilar bile duct obstructions is more contentious. Several principles of effective biliary drainage in this setting need to be kept in mind. First, it is often the case that drainage of a particular area of liver needs to be targeted. More than 30% of the functional hepatic parenchyma needs to be drained for relief of jaundice similar to the fact that approximately this volume of liver needs to be preserved after liver resection for effective liver function. As a biliary tumor progresses proximally in or along the bile ducts, it can segregate the biliary
systems draining various regions of the liver. For instance, if tumor segregates the right anterior sector of the liver from the right posterior sector and both from the left hemiliver, it may be most effective to target drainage of the left hemiliver for the best long-term palliation. Similarly, drainage of liver that is compromised by obstruction of portal inflow or atrophy is unlikely to contribute to relief of jaundice. Next, violation of any area of the liver that is not effectively drained or later becomes undrained due to progression of the tumor can be associated with the development of cholangitis. It is very common for patients with perihilar malignant bile duct obstructions to have bouts of cholangitis during the course of their disease once the biliary system is instrumented. A transhepatic percutaneous approach is often favored for perihilar malignant bile duct obstruction as it may allow more precise targeting of the specific area of liver to be drained without contaminating other areas of liver through contrast injection or inadvertent passage of wires that may occur when accessing the biliary system through the ampulla (Fig. 65-8). Some authors, however, have demonstrated that in certain experienced centers, the principles of safe and effective drainage of malignant perihilar bile duct obstructions can be followed and adequate results obtained with an endoscopic approach.

Metal stents tend to provide more durable palliation than plastic (polyethylene) stents (median stent patency of 8-12 vs 4.8 months) and are generally preferable in patients with malignant biliary obstruction. Plastic stents should be changed every 3 to 6 months to prevent episodes of cholangitis related to stent occlusion; these stents may be appropriate for patients with estimated survival durations of less than 3 months (eg, patients with diffuse metastases). Some authors have found that better outcomes are achieved when both hemilivers are drained; however, a prospective, randomized controlled trial of patients with pCCA found that unilateral biliary drainage provided adequate palliation of obstructive jaundice, and patients randomized to receive bilateral biliary stents had higher complication rates (cholangitis) but no detectable benefits. The approach therefore needs to be individualized.

For patients with pCCA who are found to have carcinomatosis at the time of exploratory laparoscopy, laparoscopic cholecystectomy traditionally has been recommended, to prevent subsequent development of acute cholecystitis related to biliary stent–induced cystic duct obstruction. The value of prophylactic cholecystectomy in this setting is unproven and should not be
routinely performed. Stenting should be performed using percutaneous or endoscopic techniques postoperatively.

For patients who are found to have unresectable disease at the time of open exploration, available evidence suggests that surgical biliary bypass offers more durable palliation than percutaneous or endoscopic stenting. Patients with unresectable dCCA should undergo hepaticojejunostomy. The palliative options for patients with unresectable perihilar cholangiocarcinoma include Roux-en-Y hepaticojejunostomy to the left and/or right hepatic ducts in the hilus of the liver if feasible, or Roux-en-Y hepaticojejunostomy to segmental/sectoral ducts away from the tumor. The segment 3 hepatic duct can be approached by following the falciform ligament into the recess of the left hemiliver in the umbilical fissure. Localization of segmental or sectoral ducts on the right side of the liver (ie, right anterior sector duct, segment 5 duct, or segment 6 duct) is very difficult as no external anatomic landmarks exist, and considerable parenchymal dissection is often necessary. Intraoperative ultrasonography (IOUS) may facilitate localization. As with endoscopic and percutaneous drainage procedures, unilateral bypasses should be avoided in the presence of ipsilateral liver atrophy or portal vein obstruction.

External beam radiation and transcatheter brachytherapy may contribute to pain relief and biliary decompression; however, the data on the effects of radiation on survival duration are conflicting.

Finally, photodynamic therapy (PDT), in which endoscopic application of light activates a photosensitizer, leading to local cell death, has been associated with promising results. One prospective randomized trial, in which 19 patients with advanced cholangiocarcinoma were randomized to stenting alone or stenting followed by PDT, was terminated prematurely because patients randomized to the PDT arm were found to have a significantly longer survival (493 vs 98 days, median survival) in addition to improved biliary drainage and quality of life.\(^88\) PDT-associated prolongation of survival was also observed in another prospective randomized trial.\(^89\) These trials were small, and application of PDT is limited by its availability. Additional study of this modality is warranted.

REFERENCES


INTRODUCTION

Minimally invasive surgery has revolutionized the way we perform surgery due to the benefits of enhanced recovery, specifically less postoperative pain and fewer wound-related complications. These surgical techniques have become widespread and the gold standard for the management of certain entities as a result of outcomes data, improved equipment (including smaller, user-friendly articulating instruments and robotic-assisted surgery), patient expectations, and the easily accessible worldwide media.

The advanced minimally invasive surgical techniques in this chapter address the role of intraoperative imaging and the management of bile tract stones, tumors, and cysts. These approaches are ideally offered in an environment where a multidisciplinary approach is provided. As the demand for less invasive and more subspecialized expertise increases, knowledge of how this field is evolving will be important in offering our patients the best clinical care with the least associated procedural risk.
INTRAOPERATIVE IMAGING

Clarifying biliary anatomy to facilitate safe surgical dissection or identifying biliary ductal injuries is essential. A meticulous dissection of the gallbladder with the “critical view of safety” approach has been used for this purpose. When this technique or other surgical approaches do not provide this information or when they cannot be performed safely, the use of intraoperative imaging such as intraoperative cholangiogram (IOC) is required. Additional indications for the use of IOC include the presence of jaundice, elevated liver function or pancreatic enzymes levels, biliary ductal dilation, or stones on imaging. A meta-analysis revealed that the incidence of unsuspected retained stones after a cholecystectomy was 4%, with only 15% of these going on to cause clinical problems. 

The probability of this pathology can be classified as low (<5%), medium (5%-50%), and high (>50%) according to bilirubin level (<1.8, 1.8-4, and >4 mg/dL), dilation of common bile duct (CBD; >6 mm), and clinical signs of cholangitis. Because small stones may pass spontaneously, a preoperative endoscopic retrograde cholangiography (ERC) is not necessary or efficient in most cases, and laparoscopic cholecystectomy with IOC will suffice to document a clear CBD during cholecystectomy; if needed, a postoperative ERC can be used for those with clinically significant residual stones. Using fluoroscopic IOC, stones can be identified with greater than 95% sensitivity and specificity, with a 5% false-positive rate and 1% false-negative rate, although these rates are highly variable depending on the study. Magnetic resonance cholangiography (MRC) has a high sensitivity (90%) and specificity (95%) for choledocholithiasis with a low-risk profile compared to ERC and thus occupies a place in the management algorithm when there is medium probability. If stones are encountered during MRC, then proceeding with preoperative ERC is recommended. If stones are not diagnosed on MRC, proceeding with a laparoscopic cholecystectomy with IOC is recommended. A proposed algorithm to address clinically suspected CBD stone is presented (Fig. 66-1).
While the information obtained from IOC is valuable, its routine versus selective use continues to be debated due to the associated increased cost from additional instrumentation and increased operating room (OR) time on the one hand and decreased readmission rates from postcholecystectomy syndrome on the other.9,10

Other forms of intraoperative imaging including ultrasonography and infrared-activated fluorescence, although used less often, are finding their way into the OR as a result of their unique advantages. Ultrasonography is highly sensitive (83%-100%) and specific (98%-100%) in identifying CBD stones and ductal dilatation and is more cost effective compared to IOC (ultrasonography machines cost $40,000-$75,000, whereas C-arms and associated supplies cost $500,000). Factors that have limited its widespread adoption include the lack of therapeutic capabilities and operator dependency.11 An approach such as indocyanine green (ICG) fluorescence
would be advantageous in avoiding radiation exposure and penetrating the biliary ductal system as needed for direct injection of a contrast dye during standard IOC. Its reported ease of use and relatively low cost are another benefit. ICG is hydrophilic and binds to albumin in plasma as well as to $\alpha_1$-lipoprotein. It is exclusively eliminated in the liver and has no metabolism. ICG is injected intravenously approximately 60 minutes prior to making a surgical incision, and when illuminated by infrared light, the dye manifests fluorescence. Limiting factors of this approach include allergies to ICG dye, inability of the infrared light to penetrate thick and or deep tissue such as what would be encountered in morbid obesity or severe inflammation, and the need for specialized imaging system equipment.\textsuperscript{12-14}

For a successful IOC, the patient should be positioned on the appropriate OR table in a way that the C-arm can have adequate access to the patient’s right upper abdomen during the laparoscopic cholecystectomy. The most common approach for an IOC is using contrast dye injected directly into the infundibulum of the gallbladder or cystic duct. Advantages of accessing the gallbladder infundibulum directly include avoiding a ductotomy on what may turn out to be the CBD instead of the cystic duct. Another advantage is its ease of cannulation compared to the relatively smaller cystic duct. Disadvantages include the possibility that the dye may not leave the gallbladder due to an occluded infundibular-cystic duct junction from an impacted stone or inflammation, tortuosity of the cystic duct, and presence of the spiral valves of Heister. In either approach, proximal occlusion with either a grasper or clip will avoid inadvertent backflow of the dye and help orient the imaging. Traction on the gallbladder will provide additional exposure and duct alignment for better imaging interpretation. The cholangiogram catheter system should be flushed thoroughly with saline prior to its use to avoid misinterpretation of the air bubbles injected into the biliary ductal system from the tubing. The imaging should include the cystic duct, left and right hepatic ducts, common hepatic duct, and CBD, and the contrast should be seen filling the duodenum. To assist with improved visualization of the proximal biliary ductal system, enhanced filling by the contrast occurs with placing the patient in Trendelenburg position and administering 1 to 2 mg of intravenous morphine to induce sphincter of Oddi contraction. Visualization of the duodenum filling with contrast can be enhanced by administering 1 mg of intravenous glucagon to allow for sphincter of Oddi relaxation. Even with ideal imaging, it is important to always use caution
because misinterpretation is possible in cases where biliary ductal injuries occur.\textsuperscript{15}

**LAPAROSCOPIC COMMON BILE DUCT EXPLORATION**

Intraoperative common duct exploration has not gained wide acceptance in the surgical community, as shown in a US survey-based study and a Swedish nationwide retrospective study.\textsuperscript{16,17} Although preoperative ERC is the predominant method of bile duct clearance in the setting of laparoscopic cholecystectomy, laparoscopic CBD exploration (LCBDE) has been shown to be a safe and effective single-stage option for the management of CBD stones due to the feasibility of successful completion laparoscopically (96%), few major complications (5%), and excellent long-term results.\textsuperscript{18,19} When compared to preoperative ERC and subsequent laparoscopic cholecystectomy, both approaches were equivalently effective in detecting and removing CBD stones and were equivalent in overall cost and patient acceptance.\textsuperscript{20,21} LCBDE does require advanced surgical expertise, longer OR time, and specialized equipment; however, LCBDE has been shown to reduce the length of hospital stay, reduce recurrent CBD stones, and eliminate the potential risks of ERC-associated pancreatitis and papillary stenosis with a single procedure.\textsuperscript{22-26} When possible, a transcystic route is preferred to the transcholedocotomy approach due to the lower incidence of bile leaks and decreased overall morbidity.\textsuperscript{27} A transcystic approach may not be feasible with anomalous anatomy, proximal stones, strictures, and large (>6 mm) or numerous (>5) stones.\textsuperscript{28} Although large (>7 mm) and impacted stones have been associated with failure of stone clearance by LCBDE and may necessitate conversion to an open CBD exploration or reliance on postoperative endoscopic retrograde cholangiopancreatography (ERCP), others have performed successful LCBDE stone extraction after failed preoperative ERC. Other factors such as adhesions and altered anatomy seem to determine LCBDE success or conversion to an open procedure.\textsuperscript{29,30} Intraoperative common duct exploration has been shown to be less effective than postoperative ERCP in terms of ductal clearance in cases of emergency surgery.\textsuperscript{31}
After accessing the cystic duct, a flexible-tip guidewire is advanced into the CBD. To allow access of the choledoscopy, a balloon catheter is used to dilate the cystic duct to 3 to 5 mm. Stone extraction proceeds in either a retrograde fashion through the cystic duct with a wire basket or in antegrade fashion by dilating the ampulla and pushing the stone through with a balloon catheter. Remaining debris should be flushed, and a completion cholangiogram should confirm clearance and identify any procedural-related ductal injuries. Traditionally a T-tube was left in place for drainage after CBD exploration, but recent studies have shown that primary duct closure following LCBDE is safe, can be employed routinely as an alternative to T-tube insertion, and has a short hospital stay and low morbidity rate.\textsuperscript{32,33}

If stones cannot be cleared during LCBDE, a temporary stent may assist in decompression in the interim while awaiting postoperative ERC. Laparoscopic transampullary stenting has been shown to be a safe and feasible technique.\textsuperscript{34}

**LAPAROSCOPY-ASSISTED ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY**

Roux-en-Y gastric bypass surgery has become a standard approach in the management of morbid obesity. This results in more challenging access to the duodenum for diagnostic and therapeutic reasons. Advanced endoscopic instrumentation such as overtubes provides additional support to guide the endoscope to otherwise inaccessible locations, but when these fail, there still remains the need for surgical access to this excluded region.\textsuperscript{35}

Technical challenges with laparoscopy-assisted endoscopic retrograde cholangiography (LAERC) may arise related to patient positioning since ERCs are typically performed with the patient in a prone position and loss of working space can occur due to bowel dilatation from endoscopic insufflation.

Another variation of LAERC includes the laparoscopic rendezvous technique of laparoscopic cholecystectomy and IOC with placement of a guidewire, which would then be used for simultaneous ERC. This approach has been shown to be feasible for the management of CBD stones during a single staged procedure. The laparoscopic positioning of the guidewire may allow reduced complications secondary to papilla cannulation.\textsuperscript{36}
LAPAROSCOPIC BILIARY BYPASS

A choledochoduodenostomy or choledochojejunostomy can be used in cases where biliary flow cannot be reestablished via the native ductal system due to impacted CBD stones. As a general approach, if the duodenum can be mobilized in a tension-free manner to a portion of nonobstructed distal CBD, a choledochoduodenostomy is favored because it requires 1 less anastomosis and still allows for postoperative endoscopic access.

A similar approach to the open technique is used during the laparoscopic choledochoduodenostomy (LCD), with exposure being provided by a liver retractor, meticulous hemostasis, and constant suctioning of bile and enteric content. A longitudinal incision is made in the center of the anterior surface of the distal CBD as close as possible to where it meets the duodenum. A longitudinal incision is made in the duodenum allowing for the anastomosis to be tented open as the corner stitches of each of these structures are placed. The length of the CBD incision is influenced by the diameter of the CBD. A small, nondilated duct may require a longer incision to avoid the need for postoperative reintervention due to anastomotic narrowing. The duodenal incision should begin as a small incision that is gradually enlarged depending on the dynamic assessment of tension and patency of the anastomosis. In general, an interrupted stitch using a small (4-0) absorbable suture is recommended to avoid narrowing and delayed stone formation. Although commercially available devices (eg, Endo Stitch, Autonomy, Laparo-Angle Articulating Instruments) and robotic technology may aid with sewing at awkward angles, most cases are amenable to free-hand sewing with laparoscopic needle drivers.

A laparoscopic hepaticojejunostomy (LHJ) may be used to reconstruct the extrahepatic biliary tract after laparoscopic choledochal cyst resection or as part of a more extensive procedure such as during a laparoscopic pancreaticoduodenectomy. For pathology of the pancreatic head and uncinate process, this procedure gives equal if not superior results compared to its open counterpart related to enhanced recovery as seen with most minimally invasive surgical procedures.37-39

Factors associated with the technical complexity of the LHJ are duct size and level of the anastomosis. A distally located, dilated common hepatic duct is more easily reconstructed than 2 separate, smaller, nondilated, proximally located left and right hepatic ducts. A segment of small bowel that is able to
reach the duct in a tension-free manner is brought through a defect in the transverse mesocolon to the right of the patient’s midline taking care to avoid injury to the vasculature and underlying duodenum. We recommend fashioning the end-to-side hepaticojejunostomy before the side-to-side jejunojejunostomy to avoid excessive anastomotic tension (Figs 66-2 and 66-3).

**FIGURE 66-2** Choledochal cyst.
Occasionally, laparoscopic biliary bypasses are required for palliative reasons such as unresectable pancreatic cancer that is causing biliary obstruction unamenable to endoscopic stenting. Pancreatic cancer is the fourth leading cause of cancer-related death in Western society.\(^\text{40}\) Eighty percent of these patients are not candidates for curative resection at the time of diagnosis, and 30% of them will present with nonmetastatic locally advanced disease.\(^\text{41}\) Most pancreatic tumors are located in the head and cause obstructive jaundice, and approximately 20% of these patients will also develop duodenal obstruction.\(^\text{42}\)

Palliation via a laparoscopic cholecystojejunostomy avoids the duodenum that may be involved in a locally obstructive process, such as the LCD, and requires less operative time compared to the LHJ thanks to the relative ease of the stapled anastomosis of the gallbladder to the Roux limb of jejunum. This technique should not be used when flow of bile thought the cystic duct cannot be confirmed.\(^\text{43}\)

Endoscopic or percutaneous palliation is advantageous due to rapid
recovery, low morbidity rates, and shorter hospital stays, whereas disadvantages include stent obstruction, duodenal obstruction, higher number of reinterventions, and shorter hospital-free survival rate. Open surgical palliation is advantageous due to longer lasting palliation and disadvantageous due to higher morbidity. Laparoscopic palliation combines the advantages of nonsurgical methods with the advantages of open surgery with an acceptable morbidity rate and low mortality rate. Although technically demanding, these procedures have been performed laparoscopically with a high initial success rate (99%), low reintervention rate (1%), and relatively low morbidity rate (12%). Endoscopically placed metallic stents are currently the best palliation method for patients with systemic disease; if stents fail, the laparoscopic approach is a viable treatment.

CONCLUSION

There is a constant evolution of both expectations of patients and trainees and technological advances with regard to minimally invasive surgery. Thanks to their feasibility, safety, efficacy, reliability, and teachability, these techniques will continue to replace their open counterparts as the standard approach to the management of biliary surgical pathology.

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This is a perspective on biliary diseases to complement the excellent chapters on biliary tract disease in this text. It focuses on areas in my experience that I believe deserve emphasis.

**TOKYO GUIDELINES FOR ACUTE CHOLECYSTITIS AND ACUTE CHOLANGITIS**

The Tokyo Guidelines (TG) provide evidence based criteria for the diagnosis and severity grading of acute cholecystitis and acute cholangitis. First published in 2007, there have been two revisions, the latest just published in 2018 (TG18). The guidelines are available in an app for smartphones, and the app is very useful in the ER and on the ward. Furthermore, standardization of criteria for diagnosis and severity grading provide a stable platform for performance of comparative outcome studies.\(^1,2\) **Tables 67-1 through 67-4 are Tokyo guidelines 2018 diagnostic criteria and severity grading for acute cholangitis and acute cholecystitis respectively.**
TABLE 67-1: TOKYO GUIDELINES 2018 DIAGNOSTIC CRITERIA FOR ACUTE CHOLECYSTITIS

A. Local signs of inflammation.
   (1) Murphy’s sign, (2) RUQ mass/pain/tenderness

B. Systemic signs of inflammation, etc.
   (1) fever, (2) elevated CRP, (3) elevated WBC count

C. Imaging findings
   Imaging findings characteristic of acute cholecystitis

Suspected diagnosis: One item in A + one item in B
Definite diagnosis: One item in A + one item in B + C


TABLE 67-2: TOKYO GUIDELINES 2018 SEVERITY GRADING FOR ACUTE CHOLECYSTITIS

Grade III (Severe) acute cholecystitis
   “Grade III” acute cholecystitis is associated with dysfunction of any one of the following organs/systems
1. Cardiovascular dysfunction (hypotension requiring treatment with dopamine $\geq 5\mu g/kg$ per min, or any dose of Norepinephrine)
2. Neurological dysfunction: decreased level of consciousness
3. Respiratory dysfunction PaO2/FiO2 ratio $< 300$
4. Renal dysfunction Oliguria, creatinine $> 2.0$ mg/dl
5. Hepatic dysfunction PT-INR $> 1.5$
6. Hematological dysfunction Platelet count $< 100,000/mm^3$

Grade II (moderate) acute cholecystitis
   “Grade II” acute cholecystitis is associated with any one of the following conditions.
1. Elevated WBC count ($> 18,000/mm^3$)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complaints > 72 hr
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

**Grade I (mild) acute cholecystitis**

“Grade I” acute cholecystitis that does not meet the criteria of “Grade III” or “Grade II” acute cholecystitis. It can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.


**TABLE 67-3: TG18/TG13 DIAGNOSTIC CRITERIA FOR ACUTE CHOLANGITIS**
A. Systemic Inflammation
   A-1. Fever and/or shaking chills
   A-2. Laboratory data: Evidence of inflammatory response

B. Cholestasis
   B-1. Jaundice
   B-2. Laboratory data: Abnormal liver function tests

C. Imaging
   C-1. Biliary dilatation
   C-2. Evidence of the etiology on imaging (stricture, stone, stent, etc.)

Suspected diagnosis: One item in A + one item in either B or C
Definite diagnosis: One item in A, one item in B, and one item in C

Note:
   A-2: Abnormal white blood cell counts, increase of serum
        C-reactive protein levels, and other changes indicating
        inflammation
   B-2: Increased serum ALP, r-GTP (GGT), AST, and ALT levels
       Other factors helpful in diagnosis of acute cholangitis
       include abdominal pain (RUQ or upper abdominal) and
       a history of biliary disease such as gallstones, previous
       biliary procedures, and placement of a biliary stent.
       In acute hepatitis, marked systematic inflammatory
       response is observed infrequently. Virological and serological
       tests are required when differential diagnosis is difficult.

Thresholds:

| A-1 | Fever                | BT > 38°C |
| A-2 | Evidence of          | WBC (×1000/μL) < 4, or >10 |
|     | inflammatory response| CRP (mg/dL) ≥ 1 |
|     |                      | T-Bil ≥ 2 (mg/dL) |
| B-1 | Jaundice             | ALP (IU) > 1.5 × STD |
| B-2 | Abnormal liver function tests | γGTP (IU) > 1.5 × STD |
|     |                      | AST (IU) > 1.5 × STD |
|     |                      | ALT (IU) > 1.5 × STD |

Abbreviations: ALP, alkaline phosphatase; r-GTP (GGT), r-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RUQ, right upper quadrant; STD, upper limit of normal value
TABLE 67-4: TG18/TG13 SEVERITY ASSESSMENT CRITERIA FOR ACUTE CHOLANGITIS
Grade III (Severe) Acute Cholangitis
Grade III acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction at least in any one of the following organs/systems
1. Cardiovascular dysfunction Hypotension requiring dopamine $\geq 5$ µg/k/min or any dose of norepinephrine
2. Neurological dysfunction Disturbance of consciousness
3. Respiratory dysfunction PaO2/FiO2 ratio $<300$
4. Renal dysfunction Oliguria, serum creatinine $>2.0$ mg/dL
5. Hepatic dysfunction PT-INR $>1.5$
6. Hematological dysfunction Platelet count $<100,000/mm^3$

Grade II (Moderate) acute cholangitis
Grade II acute cholangitis is associated with any two of the following conditions:
1. Abnormal WBC count ($>12,000/µL, <4000/µL$)
2. High fever ($\geq 39\degree C$)
3. Age ($\geq 75$ years old)
4. Hyperbilirubinemia (total bilirubin $\geq 5$ mg/dL)
5. Hypoalbuminemia ($<\text{STD} \times 0.7$)

Grade I (Mild) acute cholangitis
Grade I acute cholangitis does not meet the criteria of “Grade III (severe)” or “Grade II (moderate)” acute cholangitis at initial diagnosis.

Early diagnosis, early biliary drainage and/or treatment for etiology, and antimicrobial administration are fundamental treatment for acute cholangitis classified not only “Grade III (severe)” and “Grade II (moderate)” but also “Grade I (mild)”. Therefore it is recommended that patients with acute cholangitis who do not respond to the initial medical treatment (general supportive care and antimicrobial therapy) undergo early biliary drainage or treatment for etiology.

Abbreviation: STD, lower limit of normal value.
BILIARY DYSKINESIA

While up to 20% of adult cholecystectomies performed in the United States are for biliary dyskinesia, cholecystectomy is rarely performed for this indication in other countries. Also, one-half of patients with suspected biliary dyskinesia have improvement in symptoms over time without cholecystectomy. Exercise, proton pump inhibitors, and anticholinergics may affect outcome of quantitative cholescintigraphy, the test used to make the diagnosis. Our group has found that this test is poorly reproducible, with about 50% of patients having a normal ejection fraction of over 35% on retesting. The comments in regard to the Rome diagnostic criteria for functional biliary pain by Teitelbaum and Soper in their chapter (Chapter 62: Cholelithiasis and Cholecystitis) deserve emphasis. Patients whose symptoms strictly fulfil the Rome criteria and whose symptoms seriously affect quality of life should be considered for cholecystectomy. Large clinical studies are needed to define the role of quantitative scintigraphy and the long-term results of cholecystectomy in relation to the presence of Rome criteria.

Culture of Safety in Cholecystectomy

CRITICAL VIEW OF SAFETY

Much has been written about the Critical View of Safety (CVS). CVS should be seen as a part of a culture of safety in cholecystectomy (COSIC). It is a pillar of safety, but only one of the three pillars. One line of evidence supporting the utility of CVS is that studies that have looked at the mechanism of major biliary injury have found that CVS was not employed in patients sustaining injury. Also, there are now multiple reports involving thousands of patients in which CVS was employed and in which there were few or no misidentification injuries, ie an injury rate well below what would be expected. In these studies some patients did not have a total cholecystectomy because of operative difficulty. Biliary injuries occur more commonly when operations are made more difficult due to the presence of severe acute and/or chronic inflammation. Under these conditions secure ductal identification by the CVS may be quite challenging or not obtainable because CVS requires clearing of the inflamed hepatocystic triangle in order to demonstrate the cystic duct, cystic artery, and the cystic plate. CVS is a
rigorous method but this is a strength of the CVS method of identification. The infundibular technique, in which the funnel-shaped infundibular-cystic duct junction is the rationale for identification, is much easier to achieve than CVS. However, biliary inflammatory fusion and contraction can make the common bile duct resemble the cystic duct when this technique is used, and this increases the chance of biliary injury. The CVS method protects because when the CVS is not achievable after a reasonable trial of dissection, surgeons are more likely to realize that conditions are too risky to proceed in the usual manner. When conditions make it too difficult and risky to get to CVS there must be a safe and effective method of dealing with difficult gallbladders. Safe means without bile duct injury, and effective means without need for a second operation. Otherwise surgeons might feel pressured to push on with a risky dissection in the hepatocystic triangle in order to avoid a second procedure or perform a cholecystostomy, which will usually necessitate a second operation. That procedure is a subtotal cholecystectomy, first described in 1898. It has been shown to be an effective bailout procedure when total cholecystectomy is dangerous.  

**SUBTOTAL FENESTRATING CHOLECYSTECTOMY AND SUBTOTAL RECONSTITUTING CHOLECYSTECTOMY**

There has been terminological confusion in this area because the terms *partial cholecystectomy* and *subtotal cholecystectomy* have been used interchangeably. Also “partial” and “subtotal” are imprecise because they fail to encompass an essential element in these operations, which is whether a functional remnant gallbladder results as a consequence of performing these procedures. A new terminology has been introduced recently. In *subtotal fenestrating cholecystectomy*, the peritonealized gallbladder wall is removed, but the part of the wall on the cystic plate is left behind or only partially removed. The cystic duct is left open or sutured from the inside so that no closed gallbladder remnant remains. Biliary fistula is common after this procedure, but usually brief in duration. In subtotal reconstituting cholecystectomy, a small closed gallbladder remnant remains behind. Stones may reform in this gallbladder remnant and become the source of symptoms later, which could require a second operation, so the author favors the subtotal fenestrating operation. This operation can usually be done laparoscopically.
If CVS is one pillar of safety and subtotal cholecystectomy a second, then the third pillar is knowing when to stop trying to do a total cholecystectomy and proceed to a subtotal cholecystectomy. This has not been precisely defined, but the topic is one of intense interest. One problem in recommending a standard pathway is that the decision for abandoning the attempt to do total cholecystectomy will be affected by the experience and training of the surgeon. Fortunately, the ease and benefits of subtotal fenestrating cholecystectomy are making this choice easier.

**CHOLEDOCHAL CYSTS**

This subject is covered completely by Parikh and Lillimoe in their chapter. This is an uncommon problem in which there is still are serious gaps in our knowledge. While choledochal cysts are associated with the development of cancer, the true incidence of cancer in this disease is unknown. Part of the reason is that there have not been good population-based studies that have searched for persons with asymptomatic cysts to determine natural history. As a result, the prevalence of asymptomatic cysts in the population is unknown. With the common use of CT scans to diagnose abdominal complaints, more choledochal cysts are being discovered incidentally. Currently, patients who are diagnosed by chance are advised to have resection. This strategy, although the current standard of care, can be questioned since it implies that a screening program should be in place. Furthermore, the threshold diameter of the bile duct that should be diagnosed as a choledochal cyst has not been defined. The upper limit of bile duct diameter is about 12 mm. Occasionally an asymptomatic fusiform bile duct of diameter 15 mm or slightly larger is found incidentally. Whether these should be classified as true choledochal cysts and whether they are associated with a higher incidence of cancer is uncertain. In these borderline cases, the presence of a high pancreatobiliary junction and a long common channel may be the deciding factor in determining that these should be classified as choledochal cysts.

Strictures at the hepaticojejunostomy may occur after resection of a choledochal cyst. This is usually due to cutting too high on the cyst proximally and then having to do anastomosis to several small ducts. The problem is that it is not apparent where to cut the cyst from the outside. We advocate cutting the cyst in half at its equator so that one can look into the
cyst and cut it off leaving a cuff of tissue around the normal ducts entering the cyst. This method has been published and illustrated.8

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PANCREAS
INTRODUCTION

Acute pancreatitis can range from a mild, self-limiting process that responds to supportive care to severe disease with multiple organ failure and high mortality. Its incidence is increasing,\(^1\) and pancreatitis is one of the most common causes of hospital admission for gastrointestinal illness.\(^2\) Although most patients experience minor episodes characterized by mild parenchymal edema without organ dysfunction, response to conservative management, and complete recovery,\(^3\) approximately 20% to 25% of patients develop clinically severe acute pancreatitis. More severe episodes may progress to pancreatic necrosis, systemic inflammatory response syndrome (SIRS), multiorgan failure, clinical deterioration, and even death.\(^4\) Historically, mortality has been up to 15% in the setting of necrotizing pancreatitis and as high as 30% with infected pancreatic necrosis.\(^5\) Recent years have seen advances in the classification and management of acute pancreatitis including evidence-based guidelines and a notable shift toward nonoperative management of even the most severe cases of infected pancreatic necrosis.
Given the wide spectrum of severity, patients with pancreatitis must receive highly individualized care. Mild acute pancreatitis can generally be managed with resuscitation and supportive care including a search for etiologic factors such as gallstones. Patients with severe pancreatitis and pancreatic necrosis may require maximal support in intensive care and occasionally surgical or endoscopic debridement of the pancreas. The indications for intervention in patients with severe pancreatitis have evolved significantly in the past 2 decades. Whereas early surgical debridement was used for most patients with pancreatic necrosis in the past, a far more conservative approach was adopted with recognition that surgical debridement was not necessary in the setting of most cases of pancreatic necrosis without infection. Revision of the 1992 Atlanta Classification of acute pancreatitis to provide a newer classification to more precisely describe the clinical behavior and imaging characteristics of acute pancreatitis has allowed more uniform categorization of the disease in recent years. At the same time, the development of minimally invasive and nonsurgical approaches to necrotizing pancreatitis has led to increased consensus that most patients, including even those with the greatest disease severity, may avoid surgical debridement. This chapter reviews contemporary management strategies in acute pancreatitis, including assessment of severity, nutritional support, the role of antibiotics, and indications for intervention.

ETIOLOGY

Acute pancreatitis has been attributed to a range of etiologic factors (Table 68-1). Intra-acinar activation of trypsinogen, with subsequent activation of other pancreatic enzymes, is thought to play a central role in pathogenesis of the disease. A local inflammatory response is associated with liberation of oxygen-derived free radicals and cytokines including interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and platelet-activating factor. These mediators play an essential role in transformation of the local inflammatory response to a systemic illness.
Most cases (70%-80%) of pancreatitis are associated with gallstones or sustained alcohol abuse; the relative frequency of these 2 factors depends on the prevalence of alcohol use in the population studied. Choledocholithiasis is the most common of known mechanical factors. The majority of patients with non–alcohol-related pancreatitis will have gallstones, and many will develop recurrent acute pancreatitis if stones persist. Another known mechanical cause of pancreatitis is instrumentation of the pancreatic or biliary duct; at least 1% of patients undergoing endoscopic retrograde
Cholangiopancreatography (ERCP) develop clinically detectable pancreatitis. Several metabolic processes are associated with pancreatitis, particularly alcohol abuse. Signs and symptoms of pancreatitis can be seen in patients with prolonged alcohol use, usually after 10 years or more of heavy ingestion. Binge drinking has not been related to pancreatitis, but its development is thought to be related to consumption of over 4 to 5 drinks per day for more than 5 years. The precise mechanism of this association is not well established. Several drugs have been related to the development of pancreatitis, particularly corticosteroids, thiazide diuretics, estrogens, azathioprine, and furosemide. In approximately 10% of cases, no underlying cause can be identified. Some have suggested that occult biliary microlithiasis may be the etiology in most cases of idiopathic acute pancreatitis. Smoking was thought to be a cofactor in alcohol-related pancreatitis, although it is now recognized as an independent risk factor in the disease with risk correlating to the extent of tobacco use.

**DIAGNOSIS, ASSESSMENT, AND IMAGING**

**Diagnosis**

Early diagnosis and determination of disease severity are essential to guide appropriate therapy. Clinical diagnosis has changed very little in recent years. Clinical signs and symptoms such as upper abdominal pain, back pain, vomiting, fever, tachycardia, and leukocytosis are nonspecific. Although the classically described signs of umbilical and flank bruising may be seen with severe retroperitoneal hemorrhage (Cullen and Grey-Turner signs), these are rare in all but the most severe cases, are nonspecific, and may be seen with any cause of retroperitoneal bleeding. Therefore, diagnosis depends on clinical suspicion and demonstration of elevated plasma levels of pancreatic enzymes. In the setting of characteristic abdominal symptoms and/or characteristic imaging, serum amylase levels of amylase or lipase 3 times the upper limit of normal secure the diagnosis. Levels of both amylase and lipase peak within the first 24 hours of symptoms, and amylase has a slightly shorter plasma half-life. Serum lipase, therefore, has a slightly higher sensitivity for detection, as elevations occur earlier and last longer than serum
Furthermore, hyperamylasemia is not entirely specific for pancreatitis and is seen occasionally with other causes of abdominal pain such as tumors of the ovaries or even kidney failure. Simultaneous determination of serum lipase and amylase only marginally improves the diagnosis of acute pancreatitis. Of note, plasma levels of pancreatic enzymes are useful for diagnosis but not for prognosis or assessment of disease severity, and absolute levels have no correlation with severity.

Assessment of disease severity is important for the initiation of goal-directed therapy. However, reproducible measures of disease severity are lacking. Early evaluation is complicated by a nonspecific clinical presentation, and severe disease may present with a fulminant sepsis-like syndrome or in a relatively innocuous manner. Initial signs and symptoms with severe disease are only different in degree from edematous pancreatitis, and both severe and mild forms share the same etiologies. Attempts to identify differences in the pathogenesis of mild and severe disease have not revealed differences, and available clinical models do not accurately predict which patients will progress to severe disease.

**Assessment of Severity**

Clinical scoring systems such as the Ranson or Glasgow scores incorporate multiple clinical variables to predict outcomes, comparing variables at admission and over the subsequent 48 hours. In Ranson’s original report, the presence of 5 or 6 positive signs was associated with a 40% mortality and prolonged intensive care unit course in 50% of patients, whereas the presence of 7 or 8 signs was associated with a nearly 100% mortality. However, these systems require 48 hours from admission for full assessment, and current data suggest they are poor predictors of disease severity. The Acute Physiology and Chronic Health Evaluation II (APACHE II) system is another physiologic scoring system that estimates disease severity based on quantifying multiple variables. Higher APACHE II scores at admission are associated with higher mortality, and data may be calculated within the first 24 hours. Despite this advantage, APACHE II scores in the first 24 hours have been found to have a limited positive predictive value of only 43% for severe acute pancreatitis. Updates that include clinical assessment of obesity (APACHE-O) or additional clinical
variables (APACHE III) have been proposed, but all updates have proven to be nonspecific with high false-positive rates, are somewhat unwieldy to use, and are not commonly incorporated into practice.

Numerous individual markers have been investigated as indicators of severity. Brown et al\textsuperscript{24} and others have shown that hemoconcentration predicts parenchymal necrosis and organ failure. Persistence of hemoconcentration and azotemia despite fluid resuscitation is predictive of severe pancreatitis.\textsuperscript{25} Increases in C-reactive protein levels with disease severity at 48 hours after admission may help identify severe disease with superior sensitivity and specificity relative to other markers,\textsuperscript{26} although the delayed peak at 36 to 72 hours after admission leads to decreased efficacy for assessment on admission.

**IMAGING**

Cross-sectional imaging, particularly contrast-enhanced computed tomography (CT), plays an essential role in evaluation of the progression to severe acute pancreatitis with associated complications. CT findings of simple edematous pancreatitis include enlargement of the pancreas with loss of peripancreatic fat planes, areas of decreased density, and occasional simple fluid collections (Fig. 68-1). The Balthazar scoring system and other similar grading systems incorporate imaging findings such as pancreatic inflammation and peripancreatic collections in an attempt to correlate radiographic appearance with morbidity and mortality.\textsuperscript{27,28} CT is particularly useful in its ability to demonstrate pancreatic necrosis. From a baseline of 30 to 50 Hounsfield units (HU), viable pancreas will typically enhance by more than 50 HU with the administration of intravenous (IV) contrast. Nonviable pancreas, however, will not enhance with IV contrast (Fig. 68-2). Various criteria used to diagnose necrosis include nonenhancement of more than 30% of the pancreatic parenchyma or an area greater than 3 cm of the pancreas that does not enhance.\textsuperscript{7} Magnetic resonance imaging (MRI) is sometimes used as an alternative in patients with moderate renal impairment or an allergy to IV contrast. MRI may have comparable sensitivity and specificity to CT for diagnosis of severe acute pancreatitis,\textsuperscript{29} although MRI is less practical for the critically ill patient.
FIGURE 68-1 Contrast-enhanced abdominal computed tomography scan in a 47-year-old man with acute pancreatitis. Relevant findings include significant fat stranding of the peripancreatic tissue, with a fluid collection at the tail of the pancreas measuring approximately 4 × 4 cm. Pancreatic parenchyma enhances with intravenous contrast, with no evidence of pancreatic necrosis. (Reproduced with permission from Clancy TE, Benoit EP, Ashley SW: Current management of acute pancreatitis, J Gastrointest Surg. 2005 Mar;9(3):440-452.)
FIGURE 68-2 Contrast-enhanced abdominal computed tomography scan in the same 47-year-old man with a second episode of acute pancreatitis. Scan shows stranding of peripancreatic fat, consistent with acute pancreatitis. Most notable is the near-complete absence of pancreatic enhancement, which is diagnostic of pancreatic necrosis. (Reproduced with permission from Clancy TE, Benoit EP, Ashley SW: Current management of acute pancreatitis, J Gastrointest Surg. 2005 Mar;9(3):440-452.)

The timing of and indications for CT in acute pancreatitis require clinical judgment rather than strict criteria. CT scans performed early in the course of the disease will often fail to identify developing local complications, as necrosis may only become evident 2 to 3 days after the onset of symptoms, significantly limiting its utility at admission. The sensitivity for identifying pancreatic necrosis using contrast-enhanced CT approaches 100% after 4 days from diagnosis. It is therefore advisable to obtain an abdominal CT with IV contrast in patients with clinical and radiographic features of acute pancreatitis who do not improve after several days of conservative management. Repeat CT may be obtained with signs of clinical deterioration.

CT scan is also essential to facilitate image-guided tissue aspiration in the diagnosis of infected pancreatic necrosis. The development of infected pancreatic necrosis, as discussed below, is an indication for radiographic,
endoscopic, or surgical intervention. However, clinical criteria do not easily differentiate severe pancreatitis from infected necrosis. Leukocytosis, fever, and organ failure may be seen with or without infection. Emphysematous pancreatitis, the demonstration of gas within the pancreatic parenchyma, is diagnostic of infection but is uncommonly seen (Fig. 68-3). Image-guided aspiration of the necrotic pancreas can be used to diagnose infected pancreatic necrosis with a high degree of accuracy (Fig. 68-4). CT-guided aspiration is reserved for patients with documented pancreatic necrosis who are not improving clinically or who experience clinical decline.

FIGURE 68-3 Computed tomography scan demonstrating emphysematous pancreatitis, which is pathognomonic for infected pancreatic necrosis. Operative debridement is indicated without additional confirmation of pancreatic infection.
FIGURE 68-4  Computed tomography (CT)-guided percutaneous fine-needle aspiration (FNA) of the pancreatic tail. The aspiration area had previously been identified as necrotic in the contrast-enhanced CT shown in Figure 68-2. Gram stain and cultures were negative for organisms, consistent with sterile pancreatic necrosis. (Reproduced with permission from Clancy TE, Benoit EP, Ashley SW: Current management of acute pancreatitis, *J Gastrointest Surg.* 2005 Mar;9(3):440-452.)

The sensitivity and specificity for detection of infection with CT-guided aspiration are reported to be 96% and 99%, respectively, with a positive predictive value of 99.5% and a negative predictive value of 95%. Areas of nonenhancing pancreas are aspirated, with samples sent for aerobic, anaerobic, and fungal culture. In most patients, diagnosis of infection may be made with a positive Gram stain of the aspirate rather than waiting for confirmatory culture.

Infection may occur at any point in the clinical course with pancreatic necrosis, with the incidence of infection increasing up to 3 weeks after presentation. In one study, infection was documented in 49% of patients in the first 14 days, but less than 15% had infection diagnosed after 35 days. Infection may occur later in the course of the disease, even after a prior negative aspiration. Repeat CT-guided aspiration is therefore often necessary in the setting of clinical decline. In one series of patients with aspiration
demonstrating infection, the first aspirate was positive in 17 of 30 patients (57%), although 7 patients (23%) required 2 or more procedures and 6 patients (20%) required 3 or more aspirations to demonstrate infection.\(^\text{32}\) Fine-needle aspiration should not be performed in the absence of suspected infection due to the small risk of introducing infection into a previously sterile collection.\(^\text{33}\)

**CLASSIFICATION OF SEVERITY**

Classification of disease severity is important for the timely administration of appropriate care as well as for the assessment of treatment modalities and standardization of reporting. The Atlanta Classification emerged from an interdisciplinary symposium in 1992.\(^\text{34}\) This original Atlanta Classification defined acute pancreatitis, organ failure, and local compilations of the disease in an attempt to introduce uniformity in assessment of severity and complications. This allowed some descriptive consistency, helping to standardize clinical care and aiding clinical research. Recognition of the deficiencies of this system, particularly the failure to incorporate organ failure, led to the development of the Revised Atlanta Classification (RAC) using a Web-based iterative consultative process.\(^\text{8}\) The RAC defines categories of severity in terms of the following categories: (1) mild acute pancreatitis, with the absence of organ failure and systemic or local complications; (2) moderate acute pancreatitis, with transient organ failure and/or local complications requiring prolonged hospital stay or intervention; and (3) severe acute pancreatitis, with persistent organ failure. Another severity classification, the Determinant-Based Classification (DBC) arose from a meta-analysis of the literature.\(^\text{35}\) The DBC incorporates pancreatic necrosis in the following categories: (1) mild acute pancreatitis, with no pancreatic or peripancreatic necrosis and no organ failure; (2) moderate acute pancreatitis, with sterile pancreatic or peripancreatic necrosis and/or transient organ failure; (3) severe acute pancreatitis, with infected pancreatic or peripancreatic necrosis or persistent organ failure; and (4) critical acute pancreatitis, with infected pancreatic or peripancreatic necrosis and persistent organ failure. In addition to assessment of severity, the RAC defines specific morphologic features of acute pancreatitis and its complications (Table 68-2).
<table>
<thead>
<tr>
<th></th>
<th>Morphologic Features of Acute Pancreatitis</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Interstitial edematous pancreatitis</td>
<td>Acute inflammation of the pancreatic parenchyma and peripancreatic tissues without tissue necrosis</td>
</tr>
<tr>
<td>2.</td>
<td>Necrotizing pancreatitis</td>
<td>Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis</td>
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<tr>
<td>3.</td>
<td>Acute peripancreatic fluid collection (APFC)</td>
<td>Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis; applies to areas of peripancreatic fluid seen in the first 3 weeks after onset of interstitial edematous pancreatitis and without the features of a pseudocyst</td>
</tr>
<tr>
<td>4.</td>
<td>Pancreatic pseudocyst</td>
<td>An encapsulated collection of fluid with a well-defined inflammatory wall, usually outside the pancreas with minimal or no necrosis; usually occurs more than 4 weeks after onset of interstitial edematous pancreatitis</td>
</tr>
<tr>
<td>5.</td>
<td>Acute necrotic collection (ANC)</td>
<td>A collection containing variable amounts of fluid and necrosis associated with necrotizing pancreatitis; necrosis can involve pancreatic parenchyma and/or the peripancreatic tissues</td>
</tr>
<tr>
<td>6.</td>
<td>Walled-off necrosis (WON)</td>
<td>A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall; usually occurs &gt;4 weeks after onset of necrotizing pancreatitis</td>
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**PRINCIPLES OF INITIAL MANAGEMENT**

**Resuscitation and Monitoring**

Although patients with acute pancreatitis require management strategies...
tailored to disease severity, the initial management of patients is increasingly standardized. A cornerstone of this initial management is aggressive fluid resuscitation to replace considerable extravascular or “third space” fluid losses. Volume depletion accounts for the hemoconcentration and azotemia associated with severe pancreatitis. Animal data suggest that early aggressive fluid resuscitation prevents pancreatic necrosis, and retrospective clinical data suggest that such aggressive fluid resuscitation in the first day after admission reduces complications. While aggressive fluid administration does not necessarily prevent the progression to necrosis, patients with inadequate resuscitation have an increased risk of developing pancreatic necrosis. Fluid resuscitation is particularly important in the initial 24 hours, at rates often exceeding 200 mL/h. One randomized controlled trial suggested that the use of lactated Ringer’s solution versus normal saline reduced markers of SIRS. Close monitoring of respiratory, cardiovascular, and renal function is essential to detect and treat hypovolemia. All patients require close assessment of fluid balance, including a Foley catheter. Patients with severe disease should be admitted to an intensive care unit for continuous monitoring.

**Nutritional Support**

Historically, enteral feeding was limited in the setting of acute pancreatitis for the purpose of providing “pancreatic rest.” Enteral feeding was believed to exacerbate the existing inflammatory process through stimulation of exocrine pancreatic function and release of proteolytic enzymes. Nasogastric tubes were often used for the purpose of avoiding pancreatic stimulation and in the setting of paralytic ileus. No data support the use of nasogastric decompression in the absence of ileus, however. Although brief periods without full oral intake are common on initial presentation, limitation of nutritional intake may have serious consequences in the setting of critical illness with enhanced catabolism and negative nitrogen balance. In this setting, total parenteral nutrition (TPN) has often been used for nutritional support in an effort to prevent further complications.

Ample evidence now suggests that strict limitations on enteral nutrition are unnecessary and that, in fact, enteral nutrition may be feasible and safe even in severe pancreatitis. Enteral nutrition helps support intestinal
mucosal integrity and avoids alterations to the intestinal barrier function and altered intestinal permeability seen with TPN. Various studies comparing TPN to enteral feeding have demonstrated that enteral feeding is associated with fewer complications and improvement in inflammatory markers and severity scores. Meta-analyses of the literature have confirmed the preferential use of enteral nutrition to reduce complications, infection, and length of hospital admission.

In patients with mild disease, data support the initiation of oral feeding even before resolution of pain or normalization of pancreatic enzyme levels, and a low-fat diet has been demonstrated as safe soon after admission. The need for assisted enteral feeding due to severe symptoms or an inability to tolerate oral feeding may be recognized in the first few hospital days. Early administration of nasoenteric feeding has not been shown to be superior to waiting 2 to 3 days to see if oral feeding is tolerated. While most studies investigating the use of enteral feeding have used nasojejunal feeding, randomized trials and a meta-analysis have shown that nasogastric or postpyloric feeding is equivalent. Meta-analyses have shown no evidence to support the use of elemental or immune-enhanced feeding formulas versus standard formulas.

The Role of ERCP and Cholecystectomy

Choledocholithiasis is recognized as a major cause of acute pancreatitis and the primary cause of acute pancreatitis in most populations. ERCP has therefore been used as a diagnostic and potentially therapeutic modality in acute pancreatitis. Patients are selected for ERCP predominantly based on whether evidence exists for obstructive choledocholithiasis. The need for ERCP in the setting of biliary obstruction and cholangitis is paramount, although the need for ERCP without such evidence is less evident. Two randomized controlled trials demonstrated a significant reduction in morbidity without reduction in mortality with the routine use of ERCP in acute pancreatitis. However, both studies were criticized for including patients with known obstruction and cholangitis, possibly accounting for the observed benefit. A more recent multicenter study that excluded patients with biliary obstruction showed increased complications and mortality in the group randomized to undergo ERCP. ERCP is not indicated in the absence
of jaundice, with evidence of choledocholithiasis with a dilated bile duct on imaging, in cases of mild acute gallstone pancreatitis, or as a diagnostic test before cholecystectomy.  

Patients with gallstone pancreatitis have a high rate of recurrent disease. Several studies have documented a readmission rate of up to 18% for gallstone disease in patients admitted for acute gallstone pancreatitis and discharged without cholecystectomy. A randomized controlled trial demonstrated that patients undergoing laparoscopic cholecystectomy within 48 hours of admission for gallstone pancreatitis had a shorter hospital stay compared to waiting for resolution of pain. Early cholecystectomy is demonstrated as safe, without increases in complications or mortality, although patients with severe acute pancreatitis with signs of critical illness or pancreatic necrosis should wait several weeks prior to surgical intervention.  

High rates of recurrence in patients with gallstone pancreatitis discharged without cholecystectomy have led to the use of ERCP and sphincterotomy for risk reduction. One prospective study showed a decrease in risk of recurrent gallstone disease from 37% to 0% with ERCP and sphincterotomy. A systematic review showed reduction in all biliary events from 24% to 10% when patients not undergoing cholecystectomy underwent ERCP and sphincterotomy prior to hospital discharge. Although cholecystectomy is indicated at the index admission for gallstone pancreatitis, patients who are unable to undergo surgery due to comorbid illness should be considered for ERCP and sphincterotomy.

**Antibiotic Therapy**

The development of infected pancreatic necrosis significantly increases risk of mortality. Of patients with severe pancreatitis who succumb to the disease, most do so as a result of infectious complications, and prophylactic antibiotic therapy has been proposed in the past as a potential means of limiting infection. Infection increases over time for at least the first 3 weeks in the course of pancreatitis; in one study, 24% of patients undergoing surgery for pancreatitis had infected necrosis at 1 week, whereas 71% of patients had infection at 3 weeks. Aerobic and anaerobic gastrointestinal flora are the primary organisms involved, and infection may be monomicrobial or
polymicrobial. The association of infection with mortality has been the rationale behind the use of prophylactic antibiotics targeted against enteric organisms for patients with pancreatic necrosis. However, this practice is demonstrated to lead to the development of antibiotic-resistant bacterial and fungal infections.

Few topics in pancreatitis have been as controversial in past years as the use of prophylactic antibiotics in severe pancreatitis. Several randomized controlled trials examined the role of prophylactic antibiotics, with conflicting recommendations. Early trials, however, were criticized for methodology including high use of antibiotics in control arms, poor accrual, small numbers, and poorly defined inclusion criteria. Two more recent randomized studies were considered more definitive. Rokke et al\textsuperscript{67} showed no reduction in mortality or need for interventions with early use of imipenem, and Dellinger et al\textsuperscript{68} showed no impact on pancreatic or peripancreatic infection, intervention rate, or mortality with the use of meropenem. Meta-analyses have confirmed no reduction in mortality, intervention rate, or incidence of pancreatic infection with prophylactic antibiotics.\textsuperscript{69-71}

Despite the acceptance that antibiotics should not be used for prophylaxis, many patients still receive antibiotics in the absence of documented pancreatic infection.\textsuperscript{72} This often represents suspected sepsis from another source, treatment initiated at another institution prior to transfer to a tertiary care center, or other clinical suspicion for infection. In all settings, antibiotics should be discontinued in the absence of documented infection.

**INTERVENTION FOR PERIPANCREATIC FLUID COLLECTIONS AND PANCREATIC NECROSIS**

While interstitial acute pancreatitis is usually self-limited and managed with supportive care, approximately 20% of patients will proceed to necrotizing pancreatitis. This is notable for necrosis of the pancreatic parenchyma or peripancreatic tissue, manifestations of SIRS, risks of infection, and multiorgan failure.\textsuperscript{73} Mortality can reach 15% with pancreatic necrosis and exceed 30% with infected pancreatic necrosis.\textsuperscript{5} Local complications
identified on CT scan include peripancreatic fluid collections, acute necrotic collections (ANCs), pseudocysts, and walled-off necrosis. A number of surgical and other interventional approaches have been employed in an attempt to limit the morbidity and mortality of this process. Recent years have witnessed a significant change in the indications for intervention for necrotizing pancreatitis, timing of intervention, and methods of surgical, radiologic, and endoscopic interventions. The role of conservative management and minimally invasive approaches is now better defined, and more patients are able to avoid traditional surgical debridement with the use of percutaneous catheter drainage and endoscopic techniques. No universally accepted algorithms exist, although evidence-based consensus continues to develop.9 Data support the preferred management of patients with complications of acute pancreatitis at high-volume centers capable of offering the full multidisciplinary complement of care.74,75

Only a few decades ago, the presence of pancreatic necrosis was considered an indication for surgical debridement. It was later recognized that nonoperative management could be pursued for sterile pancreatic necrosis, with surgical debridement limited to infected necrosis.6,32,66 In this paradigm, the presence of infection was initially considered an absolute indication for surgical debridement, as infected pancreatic necrosis had been associated with a mortality of virtually 100% without debridement.76 The need for surgery in all such patients was subsequently challenged by recognition that some patients with documented infected pancreatic necrosis were successfully managed with antibiotics and maximal supportive care.77 Surgical therapy, when required, could often be delayed to a later stage of disease when the systemic inflammatory response had been stabilized and the pancreatic necrosum had become more well-defined and demarcated from surrounding tissue. Others have described series in which over half of the patients with infected necrosis are treated with nonoperative therapy,78 and urgent surgical debridement for all patients with infected pancreatic necrosis is no longer considered mandatory. While the presence or absence of infection affects prognosis and management, clinical symptoms, rather than suspicion of infection, largely dictate management. The primary modality of intervention until recently was traditional “open” surgical debridement. This has evolved to incorporate endoscopic and radiologic techniques as well as multidisciplinary management.
Pancreatic Necrosis With Infection

Many, if not most, patients with infected pancreatic necrosis will require some form of intervention. Although some asymptomatic patients with infected necrosis are successfully treated with antibiotics alone, these patients are susceptible to clinical decline and will require surgical, endoscopic, or radiographic intervention with the onset of clinical signs or symptoms that do not respond to medical management. Delayed surgical debridement was known to be far preferable to early surgery in the era of surgical management, with higher morbidity and mortality seen with early surgery. Early surgical debridement is considered an independent predictor of poor outcome in necrotizing pancreatitis. Expedited intervention may be required in patients with systemic sepsis or hemodynamic instability; otherwise, antibiotic therapy and conservative management allow further organization of the inflammatory process with delayed intervention if symptoms persist.

Delayed intervention of infected pancreatic necrosis has been greatly facilitated by the use of percutaneous catheter drains. Freeny et al in 1998 showed that some patients with infected necrosis might have surgical management delayed or completely avoided with the use of large-bore percutaneous catheters placed with radiographic guidance. A multicenter trial has validated this strategy; comparing patients randomized to standard pancreatic debridement versus a “step-up” approach, complications were lower with the step-up approach, and approximately one-third of patients were managed with catheter drainage alone.

The recognition that patients with infected necrosis do not necessarily need urgent intervention has also changed the practice of pancreatic aspiration to diagnose infection. Patients with suspected infection are increasingly managed with antibiotics and supportive care to allow less invasive and delayed management of a walled-off collection. As a result, diagnostic fine-needle aspiration is required less frequently in the management of suspected infection.

Symptomatic Pancreatic Necrosis

The role of intervention in sterile pancreatic necrosis is less clear than in cases with infection. Although most patients without infection respond to
supportive care, others may experience clinical decline including organ failure. In past years, surgical debridement was pursued by some in the setting of disease progression or failure to improve, regardless of infection.\textsuperscript{86,87} However, no universally accepted guidelines defined the criteria for intervention in this population. Some authors suggested debridement for necrosis of more than 50\% of the pancreatic parenchyma,\textsuperscript{86} rapid clinical deterioration with organ failure,\textsuperscript{88} or the presence or persistence of organ failure.\textsuperscript{89,90} Still, evidence did not support the use of any specific criteria as an absolute indication for intervention.

The process of walled-off pancreatic necrosis (WON) was previously described as “organized pancreatic necrosis.”\textsuperscript{19} In this situation, an intrapancreatic or extrapancreatic heterogeneous semisolid collection that develops in the setting of acute necrotizing pancreatitis develops an encapsulated wall.\textsuperscript{8} Some patients may experience a prolonged clinical course with persistent pain, malaise, and inability to eat, characterized as “persistent unwellness,”\textsuperscript{91} and intervention was deemed necessary in some based on symptoms.

WON in the absence of symptoms does not require intervention, regardless of the size of the collection. Symptomatic WON, however, can be characterized by pain, intestinal or biliary obstruction, and later infection. In one series, approximately 10\% of patients with sterile pancreatic necrosis underwent surgery for persistent pain and organized necrosis at a mean of 29 days after initial presentation.\textsuperscript{32}

\section*{SURGICAL AND INTERVENTIONAL PROCEDURES}

The use of various radiologic, surgical, and endoscopic interventions varies among providers and institutions, partially due to varying institutional capabilities and evolving techniques. Delayed intervention is preferable in all patients, although interventional radiologic techniques may be performed earlier in the setting of suspected infection.\textsuperscript{80} Even in the setting of infection, there is a growing trend to treat with supportive care and antibiotics unless signs of sepsis ensue, until the pancreatic collection becomes walled off.\textsuperscript{85}
Surgical Debridement

For years, laparotomy and traditional “open” surgical debridement were the only available interventions. Surgery has involved removing necrotic pancreatic and peripancreatic tissue, preserving viable pancreas, and allowing drainage for an expected pancreatic fistula. Methods include debridement with closure over drains, debridement with open packing of the pancreatic bed, or debridement with closure over irrigation drains. Although open surgical necrosectomy allows an opportunity to remove all necrotic tissue, it is not typically required and is used when less invasive measures have failed.

When open surgical debridement is indicated, exploration may be initiated with a bilateral subcostal or midline incision (Fig. 68-5). The pancreatic bed may be approached via the gastrocolic ligament or through the transverse mesocolon. An approach through the mesocolon may avoid the dense inflammatory process obscuring planes between the stomach and transverse colon (Fig. 68-6). Others have argued against this approach in order to avoid exposing the inframesocolic space to infection. Pancreatic debridement is accomplished bluntly, using finger dissection to remove necrotic tissue that easily separates from surrounding structures. Overzealous removal of tissue can result in hemorrhage. All fluid and tissue is sent for aerobic and anaerobic culture. Exposure and removal of all tissue may require access to both paracolic gutters, the pararenal spaces, retroperitoneum into the pelvis, or the gastrohepatic omentum. Surgical debridement can be followed with closed-suction drainage (Fig. 68-7), continuous closed lavage, or marsupialization of the pancreatic bed with open drainage and repeat packing in patients with severe necrosis. Comparison between these techniques is difficult given the heterogeneous nature of patients included and lack of standardization of operative indications.
FIGURE 68-5 Operative approaches to open pancreatic debridement. Either a midline or bilateral subcostal approach is acceptable.
FIGURE 68-6 Transmesocolic approach to the lesser sac. The necrotic pancreas is approached through the transverse mesocolon, to the left of the middle colic artery.
FIGURE 68-7 Irrigation and drainage of pancreatic bed. Drainage tubes are
used for technique of closed drainage or postoperative saline lavage; for open packing technique, the pancreatic bed is packed with sterile bandages.

Several indications for open surgical debridement remain. Occasionally patients will have collections that are not accessible via image-guided techniques due to overlying abdominal structures. Collections may be multifocal or persist after minimally invasive necrosectomy. Persistent symptoms attributed to these collections may warrant access via laparotomy. In all cases, surgical therapy is delayed as long as possible, which may facilitate atraumatic debridement.98

**Minimally Invasive Debridement**

The morbidity and mortality for open pancreatic debridement are considerable in most series, particularly in the setting of organ failure.99 Minimally invasive surgical debridement techniques have been described as potential alternatives in order to decrease this risk of death and complications.100 Laparoscopic approaches to pancreatic debridement are well described and may be more successful in removing all necrotic material compared to other minimally invasive methods.101 Advantages of this approach include minimizing wound complications, although it carries some risk of further peritoneal infection with pneumoperitoneum. It is recognized that these are technically challenging laparoscopic procedures, perhaps limiting their overall utility.102

The technique of video-assisted retroperitoneal debridement (VARD) uses a retroperitoneal approach via dorsal lumbotomy and an endoscope advanced in the tract of a radiographically placed drain.103 The tract is serially dilated to allow access of an endoscope or laparoscope to visualize the necrotic cavity. Extraction of the pancreatic necrosum in these cases is limited by the diameter of the access. Several interventions may be required for complete drainage, although subsequent laparotomy is required in few patients. Success with VARD has been described, with decreased morbidity and mortality compared to open debridement104; patients with necrosis extending medially or inferior to the mesentery may not be optimal candidates.

**Direct Endoscopic Necrosectomy**
Endoscopic debridement is increasingly recognized as an alternative to open surgical debridement, although its availability is limited to specialized centers. Retroperitoneal endoscopy via transgastric fenestration allows direct visual access to retroperitoneal collections.\textsuperscript{105} An approach to the necrotic collection may be obtained from the stomach or duodenum. Collections may be identified with endoscopic ultrasound if necessary and are punctured with serial dilations to allow stent placement. Necrotic tissue is evacuated using an endoscopic snare. One contemporary series from 6 US centers showed resolution of WON in 91\% of patients with endoscopic necrosectomy, with only 4\% requiring surgical debridement.\textsuperscript{106} Other reviews have suggested 76\% definitive resolution with endoscopic techniques, with a median of 4 sessions.\textsuperscript{107} Endoscopic necrosectomy has been compared to surgical necrosectomy in a small randomized trial; endoscopic necrosectomy resulted in lower postprocedural inflammation, low organ failure, and lower pancreatic fistula, as well as lower morbidity and mortality.\textsuperscript{108}

Not all patients with pancreatic necrosis are candidates for endoscopic debridement. For endoscopic access, collections are ideally not only walled off but also adjacent to the gastric or duodenal lumen. Some collections are not accessible endoscopically due to lack of abutment of the stomach or duodenum. Early collections are also not ideally suited for endoscopic access due to risk of intraabdominal spread, and multifocal collections are also less suitable for endoscopic debridement.

**Percutaneous Catheter Drainage**

Freeny first described the use of image-guided percutaneous catheter drainage (PCD) to temporize patients with pancreatic necrosis and sepsis.\textsuperscript{83} Surprisingly, half of the patients included were treated with PCD as the only intervention. Percutaneous drainage has evolved to a first-line treatment for many patients. One significant advantage of PCD is the opportunity to address symptomatic or infected necrosis before WON has developed. PCD may be useful in patients deemed unfit for surgical intervention or to address residual collections after surgical debridement. Catheters are placed under CT or ultrasound guidance, with a transperitoneal or retroperitoneal approach. Multiple catheter may be required, and repeat procedures to place new or larger catheters up to 30 Fr may be needed.\textsuperscript{109}
Solid pancreatic debris has traditionally been thought to be too thick for evacuation with drains alone; nevertheless, studies have shown that catheters are often effective without necrosectomy. A systematic review of 11 studies from 2011 showed successful management with catheters alone in over 50% of patients.\textsuperscript{110} Other studies demonstrate an approximately 50% success rate in treating necrotizing pancreatitis with PCD, whether sterile or infected.\textsuperscript{111}

The use of PCD as the first modality in a “step-up” approach to manage peripancreatic collections is increasingly being instituted. This technique uses percutaneous or endoscopic access to manage initial symptoms or infection, with use of VARD for persistent sepsis. In the PANTER trial, catheter drainage reduced morbidity with equal mortality compared to surgical necrosectomy.\textsuperscript{84} This same group in 2011 described a cohort of 639 patients with pancreatic or peripancreatic necrosis; 62% of patients were treated conservatively and 38% were treated with an intervention, either PCD, endoscopic debridement, or surgical debridement. Mortality was only 7% in the group managed conservatively versus 27% in the interventional cohort; in the group requiring intervention, 35% of patients required only catheter drainage.\textsuperscript{82}

**SUMMARY**

Acute pancreatitis, although often self-limited and managed conservatively, may progress to severe disease with sepsis, multiorgan failure, and death. Initial management is largely oriented toward relief of symptoms and preventing progression to more severe disease. Fluid resuscitation, close monitoring, and a search for inciting factors are standard. Improved recognition of severe disease and further improvements in the characterization of complications allow tailored management of complicated disease. Nonoperative management for most patients, including patients with severe disease, has become routine, and an increasing array of options including percutaneous catheter drainage and endoscopic drainage has been successfully employed to avoid the morbidity of surgery. Open surgical debridement, once considered the gold standard of management for infected pancreatic necrosis, has a more limited role, although it remains an important tool in patients who have failed other means of intervention. Future advances in minimally invasive options will likely continue to reduce the morbidity
and mortality of severe acute pancreatitis

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COMPLICATIONS OF ACUTE PANCREATITIS

John A. Windsor • Benjamin P.T. Loveday • Sanjay Pandanaboyana

INTRODUCTION

A third of all patients with acute pancreatitis develop complications, and a quarter of those patients will not survive, but recovery is now expected for the remainder because of improvements in the diagnosis and management of acute pancreatitis.¹ The complications of acute pancreatitis can be local, regional, and/or systemic. The most important determinants of the severity of acute pancreatitis are infected local complications and persistent organ dysfunction,² which are the basis for classifying acute pancreatitis severity (Table 69-1).³,⁴ This chapter focuses on the diagnosis and management of these important complications of acute pancreatitis.

TABLE 69-1: CLASSIFICATION OF ACUTE PANCREATITIS SEVERITY BASED ON LOCAL AND SYSTEMIC COMPLICATIONS, ACCORDING TO THE DETERMINANTS-BASED CLASSIFICATION¹ AND THE REVISED ATLANTA
LOCAL COMPLICATIONS

The local complications of acute pancreatitis are related to fluid collections and tissue necrosis in and around the pancreas. These were defined by the Atlanta Symposium in 1992 by the terms pancreatic necrosis, pseudocyst, and abscess. However, these terms have been confusing and new terminology has been introduced in an attempt to reflect current understanding of the pathophysiology and CT scan morphology of the disease. Changes in the morphology of local collections can occur over time and these are now defined on the basis of their content, chronicity, and whether infection is present (Table 69-2).

The revised Atlanta Classification uses a 4-week cutoff, and fluid collections present for less time are called either an acute pancreatic fluid collection (APFC) or acute necrotic collection (ANC). These acute collections can either spontaneously resolve or progress to become “walled-
off” or encapsulated, which is a reaction of the surrounding tissue to the enzyme-rich fluid. The resulting wall is usually well-defined on a CT scan after 4 weeks. A pancreatic pseudocyst is the term that has traditionally been applied to this encapsulated lesion, but it is now appreciated that the contents can be variable ranging from entirely fluid to containing solid necrotic tissue.\(^6\) When a fluid collection has developed in association with pancreatic necrosis, the revised Atlanta Classification recommends the term “walled off necrosis” (WON). The term pseudocyst has now a more restricted definition and is only applied when the content is entirely fluid and has been present for 4 or more weeks.\(^6,7\)

**Acute Pancreatic Fluid Collections**

**DESCRIPTION**

Acute fluid collections demonstrate no solid content or defined wall, and typically exist adjacent to the pancreas. These collections occur in 30% to 50% of cases and contain a mixture of inflammatory exudate and/or enzyme-rich pancreatic secretions from small side-branch ducts. The leaked pancreatic secretions can track widely through the retroperitoneum and mediastinum and may directly lead to pancreatic ascites and/or pleural effusions. The most common routes of extension are into the lesser sac, behind the pancreatic head, behind the left and right colon anterior to the psoas muscle, and into the small bowel mesentery, and may bulge through the transverse mesocolon.

**DIAGNOSIS**

Acute fluid collections usually start to develop in the first 48 to 72 hours after the onset of symptoms. Contrast-enhanced CT (CECT), magnetic resonance imaging (MRI), transabdominal ultrasound (US), or endoscopic ultrasound (EUS) can be used to confirm the diagnosis. To distinguish an APFC from ANC, or more specifically determine whether there is necrosis within the collection, it is best to use MRI or US.\(^6\) However, the presence of necrosis within a collection can often be inferred by the extent and pattern of hypoperfusion on CECT.
MANAGEMENT

Acute fluid collections usually remain sterile and resolve spontaneously.\(^8\) However, these are the precursors of pancreatic pseudocysts. Large collections of fluid around or within the pancreas are more likely to be due to disruption of the main pancreatic duct and are more likely to persist for a number of weeks or continue to increase in size.

Acute fluid collections are rarely symptomatic and do not require active treatment. Intervention by drainage (endoscopic, radiological, or surgical) risks introducing infection into a sterile collection. An asymptomatic fluid collection is managed by observation alone, and only when infection is present is drainage necessary. There is no role for diuretics or peritoneal lavage.\(^9\) Rarely, leakage from a disrupted main pancreatic duct can be treated by endoscopic or surgical intervention. Endoscopic pancreatic duct stenting can be used across the sphincter of Oddi to decrease ductal pressure and facilitate drainage into the fluid collection through the disrupted duct to drain the collection directly or across the damaged duct to redirect drainage from the collection to the duodenum and to stent the duct to reduce the risk of stricture formation. Radiological percutaneous stenting in the presence of disrupted main pancreatic duct can result in an external pancreatic fistula. There is no role for the operative treatment of APFC.

The drainage of pleural effusions in patients with acute pancreatitis should be considered in the face of compromised respiratory function or inadequate oxygenation. Chronic pleural effusions may be due to an internal pancreatic fistula and are best treated with a chest tube, nasojejunal tube feeding, and a trial of somatostatin. Persistence or recurrence will require identification of a pancreatic leak by endoscopic pancreatography. Definitive treatment may require endoscopic or surgical internal drainage once a pseudocyst has developed, or rarely a distal resection of the pancreas if this will address the fistula.

Acute Necrotic Collections

DESCRIPTION

ANCs contain both solid material and fluid, but are not walled off by a fibrous capsule. A CECT will demonstrate hypoperfused pancreas associated
with a fluid collection. The necrosis is associated with disruption to branch ducts and sometimes the main pancreatic duct. Over time the necrotic tissue demarcates, sequesters, and liquefies, forming part of the APFC. With persistence and maturation, an encapsulating wall forms, and after 4 weeks this is termed WON. Postnecrotic collections are usually sterile but infection can occur. The term *pancreatic abscess* has been abandoned because it does not distinguish between an infected acute fluid collection (AFC), infected pseudocyst, infected ANC, or infected WON.

**DIAGNOSIS**

Acute postnecrotic fluid collections are diagnosed by CECT, MRI, US, or EUS and usually after the first week from disease onset. An infected APFC can be diagnosed by the presence of gas within the collection on CT (Fig. 69-1) within 4 weeks of disease onset. The definitive diagnosis of infected APFC requires image-guided fine-needle aspiration (FNA) for Gram stain and culture or culture of fluid obtained from percutaneous drainage. In practice a FNA is rarely required to confirm infection. Endoscopic retrograde cholangiopancreatography (ERCP) can be used to determine whether there is any ductal communication associated with the collection, but this is rarely required and risks the introduction of infection.
FIGURE 69-1  CT scan showing infected pancreatic necrosis with gas within the collection on cross-sectional (A) and coronal (B) views.

Pseudocyst

A pseudocyst is a circumscribed collection that contains only fluid, has a well-defined wall, and has been present for 4 or more weeks after disease onset. In the original Atlanta Classification, a pseudocyst was defined as a collection of pancreatic juice enclosed by a wall of fibrous tissue, and there was no mention of the content. In practice, the lesion is either a fluid collection that does not contain necrosum, which when mature is best termed a pseudocyst, or a postnecrotic fluid collection that contains necrosum, which when mature is best termed WON. The result of this redefinition is that the term pseudocyst is applicable less frequently.

The precursor of a pseudocyst is the APFC, and it is differentiated from the latter by the presence of a well-defined wall (capsule) without an epithelial lining. This is in contrast to cystic neoplasms of the pancreas, which are characterized by an epithelial lining. This, however, is not an absolute distinction, as there may be discontinuous epithelium within cystic neoplasms (probably due to pressure atrophy) and partial epithelialization within chronic pseudocysts (facilitated by communication with the main pancreatic duct). In fewer than 20% of cases, more than one pseudocyst is present. Acute pseudocysts are located most often in close proximity to the pancreas, especially in the lesser sac (Fig. 69-2), but can be found in the pelvis, scrotum, mediastinum, or thorax.
FIGURE 69-2 A CT scan of a pancreatic pseudocyst located in the lesser sac. P, pseudocyst; S, stomach.

PATHOGENESIS AND CLASSIFICATION

The development of a pseudocyst requires pancreatic duct disruption. This occurs with acute pancreatitis in 10% to 15% of cases, but also in the case of pancreatic duct trauma (usually to the pancreatic neck), and in chronic pancreatitis where there may be multiple pseudocysts due to duct obstruction. The leakage of enzyme-rich secretion incites a marked inflammatory reaction in the retroperitoneum, peritoneum, and serosa of adjacent viscera. As a result, the fluid is contained by a developing layer of granulation tissue and fibrosis that matures over time. If the communication between pancreatic duct and pseudocyst persists, the pseudocyst can continue to enlarge. The contents of the pseudocyst usually consist of a relatively clear, watery fluid. However, with hemorrhage it may contain clot and become xanthochromic. In the presence of infection, a pseudocyst will contain pus. If a fluid collection develops in the context of pancreatic necrosis, and it will contain solid tissue and should be termed WON.

Pseudocysts were classified by D’Egidio in 1991 (Table 69-3). Type I
Pseudocysts occur after an episode of acute pancreatitis and are associated with normal pancreatic duct anatomy, and rarely communicate with the main pancreatic duct. Type II pseudocysts occur after an episode of acute or chronic pancreatitis and have a diseased but not strictured pancreatic duct, and there is often a communication between the duct and the pseudocyst. Type III pseudocysts occur in chronic pancreatitis and are always associated with a duct stricture and a communication between the duct and the pseudocyst.

**TABLE 69-3: THE D’EGIDIO CLASSIFICATION OF PANCREATIC PSEUDOCYSTS AND THE PRIMARY TREATMENT OPTIONS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Context</th>
<th>Pancreatic Duct</th>
<th>Duct–Pseudocyst Communication</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute postnecrotic pancreatitis</td>
<td>Normal</td>
<td>No</td>
<td>Percutaneous drainage</td>
</tr>
<tr>
<td>II</td>
<td>Acute-on-chronic pancreatitis</td>
<td>Abnormal (no stricture)</td>
<td>50:50</td>
<td>Internal drainage or resection</td>
</tr>
<tr>
<td>III</td>
<td>Chronic pancreatitis</td>
<td>Abnormal (stricture)</td>
<td>Yes</td>
<td>Internal drainage with duct decompression</td>
</tr>
</tbody>
</table>

**COMPLICATIONS**

Complications occur in about 10% of pseudocysts. The four most common complications of pseudocysts are infection, rupture, bleeding, or symptoms due to a mass effect.\(^{12}\)

Pseudocysts are initially sterile, but infection can occur in up to 25% of cases.\(^{12,13}\) The presence of sepsis due to an infected pseudocyst is an indication for drainage (see below).

The rupture of a pseudocyst can occur by erosion into adjacent organs, which may allow the pseudocyst to resolve or it may produce an internal cystoenteric fistula or fistula between the pancreas and other organs, including pleura, bronchus, and bladder. The term fistula is technically incorrect since the communication is not between two epithelial-lined structures. Rupture into the gastrointestinal tract may be associated with significant hemorrhage. Rupture into the peritoneum leads to pancreatic ascites and can be a dramatic presentation with acute abdominal pain and rigidity from chemical peritonitis.

Bleeding associated with a pancreatic pseudocyst can be life-threatening complication. There are several causes of bleeding. Bleeding may occur
secondary to erosion and rupture into the gastrointestinal tract and presents as hematemesis and/or melena. More ominous is bleeding for the direct erosion of a significant visceral vessel, including the splenic, gastroduodenal, and middle colic vessels. The action of pancreatic enzymes (especially elastase) on the vessel wall can lead to thinning of the vessel wall with aneurysm and pseudoaneurysm formation (Fig. 69-3). This situation carries a high mortality (~20%).\textsuperscript{14} The risk of bleeding is increased in the presence of local infection. If time and patient stability permit, it may be possible to perform a CT scan with arterial phase contrast to demonstrate the pseudoaneurysm and sometimes active bleeding. However, emergency selective splanchnic angiography is frequently required to delineate the site of bleeding and to embolize the culprit vessel, which is the preferred treatment (Fig. 69-4). Bleeding into a mature pseudocyst may be arrested by tamponade, although with less mature pseudocysts there is the risk of pseudocyst rupture with hematoma. Emergency surgery is rarely required and is often very difficult where the objective is to oversew the bleeding vessel. The options then include packing if there are concerns regarding recurrent bleeding. Occasionally it is possible to resect the pseudocyst with the body/tail of the pancreas, which is effective in preventing recurrent hemorrhage.
FIGURE 69-3  A contrast CT scan showing the pseudocysts, the medial one complicated by a pseudoaneurysm related to the splenic artery.
A large pseudocyst may exert a mass effect and thereby produce early satiety (stomach), partial or complete intestinal obstruction (duodenum, gastric outlet, esophagogastric junction, and rarely small or large bowel), cholestasis (bile duct), and venous thrombosis (portal, superior mesenteric, and splenic veins) leading to portal or segmental hypertension and varices. Mass effect is more likely when a pseudocyst is greater than 6 cm in diameter.\(^\text{12}\)

**DIAGNOSIS**

With modern imaging there is a higher proportion of asymptomatic pseudocysts diagnosed. A pseudocyst may be suspected when a patient with acute pancreatitis fails to recover after the initial week of treatment or when, after initial improvement, symptoms return. In this setting there can be a moderate secondary rise in serum amylase/lipase. While a CECT is often performed, depending on the patient’s habitus and how much intestinal gas is present, ultrasonography can often make the diagnosis, and has the advantage of confirming whether the content is fluid only or whether there is solid necrosum present. EUS can be useful in distinguishing a pseudocyst from a cystic neoplasm because it often delineates internal septation better than CT scan.\(^\text{15}\) The advantage of CT scanning is that it is not operator dependent and is more useful in planning therapy. It will demonstrate the key features of a pseudocyst (ie, size, shape, wall thickness, and contents), the nature of the pancreas (ie, presence and extent of necrosis, diameter of pancreatic duct, and features of chronic pancreatitis, including atrophy and calcification), and, importantly, the relationship of these to the surrounding organs (Fig. 69-2), which is essential for planning internal surgical drainage. Triphasic helical CT scanning will delineate the regional arteries (to look for pseudoaneurysm formation) (Fig. 69-3) and veins (to look for thrombosis, cavernous transformation, and formation of varices).

ERCP is not routinely required as part of the diagnostic workup for pseudocysts. Over 90% of patients with a pseudocyst have some abnormality of the pancreatic duct, but not all require treatment. In symptomatic cases where treatment is likely, it is useful in planning further management and can
be both diagnostic and therapeutic. Because of the risks of exacerbating pancreatitis, perforation, bleeding, and introducing infection, it is best that ERCP is done within 48 hours of any planned drainage procedure. The unique diagnostic contribution of ERCP is to accurately delineate a communication between the main pancreatic duct and the pseudocyst, which occurs in up to a half of patients. A communication of this type is a relative contraindication to external drainage of a pseudocyst. The classification of the main pancreatic duct by ERCP has been shown to assist in selecting the type of treatment, where the presence or absence of a stricture, communication, and obstruction is an important feature to note. Magnetic resonance cholangiopancreatography (MRCP) may be used to assess pancreatic and biliary duct morphology instead of ERCP and in some centers has replaced ERCP in its diagnostic role. MRCP has the advantage of being noninvasive with similar diagnostic accuracy to ERCP, but lacks any potential therapeutic intervention.

Diagnosing a complication in a known pseudocyst is usually straightforward. The rupture of a pseudocyst into the peritoneal cavity is associated with the onset of acute abdominal pain and signs of peritonitis. This is in contrast to the spontaneous decompression of a pseudocyst into an adjacent organ, which usually results in the relief of symptoms. Infection of a pseudocyst is accompanied by signs of sepsis. Infection can be confirmed with image-guided FNA for Gram stain and bacterial culture. Bleeding usually results in an increase in abdominal pain and possible syncope, tachycardia, and hypotension. A drop in hemoglobin concentration is expected.

Although cystic neoplasms are rare, they can be mistaken for pseudocysts. Absence of an antecedent history of acute pancreatitis, elevation of cyst fluid carcinoembryonic antigen (CEA) or carbohydrate antigen (CA 19-9), and/or the presence of internal septations should suggest this diagnosis. If EUS is available, it will enable the identification of septations (usually microcystic pattern for serous lesions or macrocystic pattern for mucinous lesions), mural nodules, echogenic debris, and calcification. It may also allow aspiration of fluid content for analysis. Pseudocysts usually contain fluid with elevated amylase (>5000 U/mL) and an absence of tumor markers, but this should not be relied upon for a definitive diagnosis.
**INDICATIONS FOR INTERVENTION**

The natural history of a pseudocyst is not easy to predict. Spontaneous resolution occurs frequently and usually within 6 weeks. Size alone is a poor predictor because resolution can occur even with very large pseudocysts. When larger than 6 cm in diameter and in the case of continued enlargement, a pseudocyst is more likely to persist and develop complications. Persistence is also more likely if there is a distal stricture of the main pancreatic duct and a proximal communication between the main pancreatic duct and the pseudocyst.

The two principal indications for treating pancreatic pseudocysts are to relieve symptoms and to treat complications. In the absence of symptoms or evidence of enlargement, conservative management is usually reasonable. A traditional approach that dictated treatment of all pseudocysts that have been present for more than 4 to 6 weeks is no longer justified. The clinical decision about whether a pseudocyst in a particular patient requires active intervention can be difficult. The desire to allow time for spontaneous resolution to occur must be balanced against the risk of complications while waiting for cyst wall maturity. The traditional indication for treatment was the development of pseudocyst complications. Now the motivation is to prevent complications. An enlarging asymptomatic pseudocyst that has been present for 6 weeks is usually treated. A natural-history study from India indicates that asymptomatic pseudocysts less than 7.5 cm in diameter and without internal debris will resolve spontaneously on an average of 5 months. The mean diameter of pseudocysts requiring treatment is about 9 cm. While there has been a trend toward conservative management, there has been an increase in the number of ways to treat a pseudocyst, including open surgical, laparoscopic, endoscopic, and radiological techniques.

Two important rules in the treatment of pseudocysts are that a cystic neoplasm must not be treated as a pseudocyst and elective external drainage should not be done if there is downstream and unrelieved pancreatic ductal obstruction because of the high risk of an external pancreatic fistula. The approach to treatment (Table 69-4) depends on the features of the pseudocyst, the state of the main pancreatic duct (eg, stricture or communication), and the fitness and level of symptoms of the patient. Also important is the level of available expertise and experience with the various treatment modalities.
The following general features of a pseudocyst are important in considering the most appropriate treatment:

- The thickness of the pseudocyst wall, which is usually a function of the duration of the pseudocyst. This is important because adherence of the wall is more likely with maturity and is relevant for wall-opposing metal stents and for safely securing sutures for surgical drainage procedures.
- The location of the pseudocyst. If adherent to the stomach or duodenum, the options are different than if the pseudocyst is deep within the retroperitoneum and covered by bowel loops.
- The contents of the pseudocyst. The presence of blood may indicate the need for prior embolization of a pseudoaneurysm. Pus will require drainage, either internally or externally. The presence of solid necrosum suggests the lesion is in fact WON and may require some form of necrosectomy.
- The number of pseudocysts. If multiple pseudocysts are present, then minimally invasive approaches are less feasible. Conservative management is less appropriate for multiple pseudocysts.

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic</td>
<td>Transgastric drainage ± self-expanding metal stent</td>
</tr>
<tr>
<td></td>
<td>Transduodenal drainage ± self-expanding metal stent</td>
</tr>
<tr>
<td></td>
<td>Transpapillary stent</td>
</tr>
<tr>
<td>Radiologic</td>
<td>Percutaneous drainage</td>
</tr>
<tr>
<td></td>
<td>Percutaneous transgastric drainage</td>
</tr>
<tr>
<td>Surgical (open or laparoscopic)</td>
<td>Cystogastrostomy</td>
</tr>
<tr>
<td></td>
<td>Roux-en-Y cystojejunostomy</td>
</tr>
<tr>
<td></td>
<td>Cystoduodenostomy</td>
</tr>
<tr>
<td></td>
<td>Distal pancreatectomy ± splenectomy</td>
</tr>
<tr>
<td></td>
<td>External tube drainage</td>
</tr>
</tbody>
</table>
• The etiology of the pseudocyst. If there is evidence of acute-on-chronic pancreatitis, different treatment may be required than if it has arisen after the first episode of acute pancreatitis.

• The main pancreatic duct anatomy and degree of disruption. The pancreas and the pancreatic duct require separate consideration in planning the treatment of a pseudocyst. The pancreas may warrant treatment in its own right, especially if there is a ductal stricture, a dilated duct, regional disease, or a mass warranting resection.

**TREATMENT OPTIONS**

Although there has been a trend toward more conservative management of pseudocysts, especially in the absence of symptoms or complications, there has been an increase in the number of treatment options available (Table 69-5). The most effective and reliable means of treating a pseudocyst is probably still by internal drainage by an open surgical approach, but there is a lack of comparative studies between surgical, endoscopic, and radiological treatments. Despite this, less invasive options are now being used more frequently.

**TABLE 69-5: OPEN AND MINIMALLY INVASIVE APPROACHES TO THE TREATMENT OF PANCREATIC NECROSIS**

**Open surgery approaches**
- Pancreatic resection
- Necrosectomy + wide tube drainage
- Necrosectomy + relaparotomy (staged reexploration)
- Necrosectomy + drainage + relaparotomy
- Necrosectomy + laparostomy ± open packing
- Necrosectomy + drainage + closed continuous lavage

**Minimally invasive approaches**
- Laparoscopic necrosectomy
- Laparoscopic intracavity necrosectomy
- Laparoscopic-assisted percutaneous drainage
- Laparoscopic transgastric necrosectomy
Radiological Treatment. The first description of direct percutaneous aspiration and external drainage using radiologic guidance was in the early 1980s. This technique has become widely practiced, with a reported morbidity of between 10% and 30%. It can be used with an immature pseudocyst wall, although the risk of complications is higher in this setting. Percutaneous drainage is best suited to D’Egidio type I pseudocysts in which there is no significant underlying duct abnormality or communication between the duct and pseudocyst. In simple, uncomplicated pseudocysts, percutaneous drainage is usually successful but is rarely necessary since this group is rarely symptomatic, has the lowest complication rate, and has the best chance of spontaneous resolution.

The introduction of a transgastric approach to percutaneous drainage has almost abolished the problem of external pancreatic fistulas (Fig. 69-5). This produces a percutaneous cystogastrostomy but requires an initial period of external transgastric drainage and then subsequent internalization at about 2 weeks. Internalization can be facilitated with a concurrent endoscopic view, especially when using double pigtail catheters. Endoscopy is used to remove the catheters when the pseudocyst has resolved on imaging. A well-matched population-based study comparing percutaneous (n = 8121) with open surgical drainage (n = 6409) in 14,914 patients with pancreatic pseudocysts revealed a longer length of hospital stay and twice the mortality (5.9 vs 2.8%) for percutaneous drainage. Currently there is a limited role for percutaneous catheter drainage of pseudocysts, but this is most likely to be used in unfit patients and those who are unstable with an infected pseudocyst.
Endoscopic Treatment. There has been significant upsurge in the use of endoscopic treatment for pseudocysts over the last decade. Endoscopic transmural drainage is now widely used. It is wise to perform cross-sectional imaging first to ensure sound apposition of cyst and stomach. While a visible bulge from the pseudocyst may be apparent on endoscopy, EUS guidance during these procedures is now the standard of care. EUS allows greater accuracy and safety by confirming the anatomic route, assists in ruling out a cystic neoplasm, and can identify blood vessels, reducing the risk of bleeding. There are several options available once the cyst is punctured and a guidewire inserted into the cavity. If there is no solid material found in the pseudocyst, then a single pigtail catheter might be all that is required. Recurrence is a risk, especially if there is underlying communication with the main pancreatic duct. While multiple pigtail stents can be inserted following balloon dilation of the track, it is now preferable to insert a self-expanding metal stent designed for transgastric drainage. A recent advance is the lumen-apposing design to reduce the risk of cyst content leaking into the lesser sac (Fig. 69-6). These metal stents are removed endoscopically after pseudocyst resolution. Endoscopic transpapillary techniques include stenting the sphincter of Oddi to lower ductal pressures and to treat pancreatic ducts strictures. The stent can also be advanced via the pancreatic duct into the pseudocyst when there is a demonstrable communication.
These endoscopic methods are still evolving but have a reported success rates over 90% with experienced practitioners, in well selected patients. Caution needs to be exercised because of the risks of perforation, peritonitis, bleeding, and infection. The risk of bleeding is significantly reduced when the initial puncture is guided by EUS.

**Open Surgical Treatment.** There is no single surgical procedure that is appropriate for all pseudocysts, and the rise of less invasive approaches has resulted in fewer operations being performed for more limited indications. Open surgery is now rarely required for a pseudocyst but may be used to
manage complications from other interventions. As with other treatments, an important factor dictating the choice is available expertise and equipment.\textsuperscript{24}

In principle, drainage operations are preferred to resection because they preserve pancreatic function, are technically easier, and have a lower mortality rate. A D’Egidio type II pseudocyst with a mature wall is best treated by internal drainage, particularly when ductal disruption or stricture is present. Recurrence rates should be less than 5%, and mortality should be less than 2%. The pseudocyst can be drained into the stomach, the duodenum, or the jejunum. The choice of surgical procedure depends on the location of the pseudocyst and its relationship to these organs.

A cystogastrostomy is ideal when the pseudocyst is adherent to the posterior stomach and indenting it (Fig. 69-7). A longitudinal anterior gastrostomy is followed by the stepwise excision of a disk (~2 cm diameter) of stomach with subjacent pseudocyst wall. The tissue is sent for frozen section in all cases to exclude cystic neoplasia. Sutures are placed in stages to reduce the risk of edge bleeding as the disk is excised. Prior confirmation of the location of the pseudocyst may be required by needle aspiration, although it is usually obvious. The stoma should be large enough to allow transgastric débridement of any necrotic tissue if the collection proves to be WON rather than a pseudocyst. The disadvantage of the cystogastrostomy is that it is not a dependent stoma, and may act as a sump that allows accumulation of gastric debris. An alternative is a Roux-en-Y cystojejunalostomy (Fig. 69-8) which is particularly suited to drainage of pseudocysts arising from the body and tail of the pancreas, when it is not adherent to the stomach and when it is bulging through the left transverse mesocolon.
FIGURE 69-7 Internal drainage of a pseudocyst through the posterior wall of the stomach (cystogastrostomy).
Combining internal drainage of a pseudocyst with a lateral pancreatojejunostomy should be considered in patients with chronic pancreatitis and a dilated pancreatic duct because it will improve outcome without increasing the risk of the procedure. The blind end of the Roux limb should be placed toward the tail of the pancreas because this allows the head of the pancreas to be drained and the bile duct to be bypassed using the same limb, if required.

Distal pancreatic resection has a role, particularly when the head of the pancreas is relatively preserved. An endoscopic retrograde pancreatogram will help to define the extent of optimal resection. If there is no pancreatic duct obstruction there are very low recurrence and fistula rates.

External surgical drainage of a pseudocyst has a very limited role in critically ill patients where radiological or endoscopic drainage is not technically feasible and the risk of a controlled external fistula is an acceptable outcome. Other rare indications for external drainage at the time of laparotomy include the control of an immature ruptured pseudocyst, and for some bleeding pseudocysts where there has been oversewing of the bleeding point. An external fistula may resolve more rapidly with placement of a transpapillary stent and with the adjunctive use of a long-acting somatostatin analogue.

**Minimally Invasive Surgery.** All open surgical techniques can now be performed using a laparoscopic approach. Intraluminal laparoscopic surgery, where the trocars are placed through the abdominal and stomach walls, has been successful. The cystogastrostomy can be performed with a stapler or by suture. A more recent modification of this approach is the mini-laparoscopic cystogastrostomy using a 2-mm intraluminal laparoscope. The view is augmented by the insertion of an oral flexible endoscope, which also can be used to explore the cyst cavity.

The balloon dilatation of a percutaneous catheter track using a similar approach to that used for percutaneous nephrolithotomy is feasible in many cases. It is worth considering this when the initial radiologic attempts have failed to bring resolution. The placement of a sheath then allows the insertion of an operating nephroscope to enable débridement of the pseudocyst and
removal of organized pancreatic necrosis and infected necrosum. This procedure can be repeated and allows the placement of a soft large-bore external drain.

**Summary of Treatment for Pseudocysts.** The treatment of choice for pancreatic pseudocysts depends on a number of factors, including size, number, and location of pseudocysts; whether the main pancreatic duct is obstructed or communicates with the pseudocyst; and whether there are complications of the pseudocyst. The clinical context is important (see Table 69-2). With the range of approaches to treatment and the variation in the availability of equipment and expertise, it is necessary to develop a rational treatment algorithm that is appropriate for the clinical setting and the patient (see Fig. 69-9). In practice, type I pseudocysts can usually be managed conservatively. Percutaneous drainage should be considered if the pseudocyst becomes symptomatic or infected. Type II pseudocysts are best managed by internal drainage, especially when there is communication between duct and pseudocyst. Endoscopic, laparoscopic, and radiologic approaches have an emerging role in expert hands. With type III pseudocysts, consideration needs to be given to decompression of the pancreatic duct and relieving the stricture at the same time as drainage of the pseudocyst.
Pancreatic Necrosis

Necrosis may involve the pancreatic parenchyma and/or the peripancreatic tissue, and this differentiates necrotizing pancreatitis from edematous pancreatitis. Initially poorly demarcated, the solid necrosis gradually liquefies and becomes surrounded by a capsule, such that after 4 weeks it is termed WON. This partially solid and partially fluid, encapsulated lesion has been described in the literature by a range of terms, including organized necrosis, necroma, and pancreatic sequestrum. The extent of tissue necrosis is not fixed and may progress, especially as the disease evolves over the first 1 to 2 weeks. The necrotizing process can extend widely to involve retroperitoneal fat, small and large bowel mesentery, and the retrocolic and
perinephric compartments. The presence of necrosis usually determines a more severe and protracted clinical course lasting weeks to months. From a clinical viewpoint, the development of necrosis is an important event in the course of acute pancreatitis because subsequent complications, both local and systemic, are associated with this.

**EPIDEMIOLOGY**

The incidence of acute pancreatitis exhibits marked regional differences, and has been reported to from 5 to 80/100,000. The proportion of patients with acute pancreatitis who develop pancreatic necrosis is approximately 20%, and of these 25% to 70% will develop infected necrosis. The risk of infection is higher when necrosis is more extensive (ie, ~30% of the gland). In addition, the risk of infection increases with time, from 24% by the end of the first week of illness to 36% at the end of the second week, and to 71% by the end of the third week. The overall mortality of edematous pancreatitis is 1% or less, that of sterile necrosis is 5%, and that of infected necrosis is 10% to 25% in the best published series.

**PATHOGENESIS**

Of the patients who develop pancreatic necrosis, 70% have evidence of it by 48 hours of the onset of abdominal pain, and all of them by 96 hours. The premature activation of proteolytic enzymes within the acinar cells and interstitium of the lobule results in extensive necrosis of pancreatic tissue and the substantial accumulation and activation of leukocytes. There are a number of factors that contribute to the failure of the pancreatic microcirculation, which is evident histologically as stasis and/or thrombosis of intrapancreatic vessels. The failure of the pancreatic microcirculation leads to ischemia, which compounds the enzymatic and inflammatory injury and leads to the full syndrome of necrotizing pancreatitis. During this first week or so, in the so-called early or vasoactive phase, there is the release of proinflammatory mediators that contribute to the pathogenesis of pulmonary, cardiovascular, and renal insufficiency. This early systemic inflammatory response and multiorgan dysfunction are frequently present with evidence of pancreatic infection. In the septic or late phase, which occurs in most patients after 3 to 4 weeks, these systemic events usually occur as a consequence of infected
pancreatic necrosis. Mild edematous pancreatitis does not usually progress to necrotizing pancreatitis, implying that pathophysiological events soon after the onset of the disease are decisive in determining the course of the disease. Necrotic lesions are most likely to permit entry of bacteria when they are demarcated by only a thin rim of granulation tissue (4-20 days). Over time, necrotic areas slowly resolve and are replaced by fibrotic scar tissue (necrosis-fibrosis sequence).

MICROBIOLOGY OF INFECTED NECROSIS

Pancreatic necrosis is most likely to become infected during the late phase of acute pancreatitis, with a median time from hospital admission to infection of 26 days. There are five routes by which bacteria might infect pancreatic necrosis: (1) hematogenous, (2) transpapillary reflux of duodenal content into the pancreatic duct, (3) translocation of intestinal bacteria and toxins via the mesenteric lymphatics to the systemic circulation via the thoracic duct, and possibly directly to the pancreas via lymphatic connections between the intestine and pancreas, (4) reflux of bacteriobilia via a disrupted pancreatic duct into the necrotic parenchyma, and (5) transperitoneal spread.

Cultures of infected pancreatic necrosis are polymicrobial in approximately one-third of patients and monomicrobial in two-thirds of patients. Gram-negative aerobic bacteria are the most common organisms identified (eg, Escherichia coli, Pseudomonas, Proteus, and Klebsiella), followed by gram-positive bacteria (eg, Enterococcus, Staphylococcus aureus). Anaerobic bacteria are identified in only around 5% of positive cultures, although this probably reflects inadequate culture techniques. Fungi may also be cultured, and are more common after use of prophylactic antibiotics. The spectrum of bacteria cultured from infected necrosis demonstrates that enteric bacteria dominate, suggesting bacterial translocation is an important event in the pathogenesis of infected pancreatic.

PREDICTION AND DIAGNOSIS

The presentation of pancreatic necrosis is usually nonspecific, with abdominal pain, distension, guarding and associated low-grade fever, and
tachycardia. The severity of pain and the extent of hyperamylasemia do not

correspond with the severity of acute pancreatitis or the extent of pancreatic
necrosis. The classic skin signs of retroperitoneal necrosis, including
discoloration of the navel (Cullen sign), the flanks (Grey-Turner sign), and
the inguinal region (Fox sign), are rare and often not seen until the second or
third week after disease onset. Patients presenting late with severe or critical
disease will often have established multiorgan dysfunction. The diagnosis of
pancreatic necrosis requires more than just clinical acumen.

Predicting the severity of acute pancreatitis and the presence of pancreatic
necrosis remains an imprecise science. Scoring systems, such as Ranson,
Glasgow, APACHE II, or “bedside index for severity in acute pancreatitis”
(BISAP), are often used for severity stratification, but are rarely better than
70% accurate. Patients with predicted severe disease and high likelihood
of pancreatic necrosis require radiological confirmation of the presence and
extent of necrosis, which is conventionally categorized as less than 30%, 30%
to 50%, and greater than 50% of the pancreas. Dynamic contrast-enhanced
CT (CECT) is the gold standard for diagnosing pancreatic necrosis and other
local complications, but is not usually indicated within the first 48 to 72
hours after the onset of acute pancreatitis. Pancreatic hypoperfusion is
usually established by about 72 hours and imaging before then probably
underestimates the extent of necrosis and the ultimate disease severity.

Current guidelines recommend that CECT is indicated for patients with
persisting organ failure, signs of sepsis, or clinical deterioration 6 to 10 days
after admission. Other imaging modalities have been developed to diagnose
the extent of pancreatic necrosis, including MRI and echo-enhanced
ultrasound (EEU), which are at least as accurate as CECT in diagnosing and
determining the extent of pancreatic necrosis. In practice, the indications
to diagnose and determine the extent of pancreatic necrosis with CECT are
when a patient fails to improve with initial resuscitation and/or when the CRP
has crossed the predictive threshold (see later). CECT can be used to score
the severity of acute pancreatitis by the CT severity index as proposed by
Balthazar, but is no better than other methods. It is important to recognize
the limitations of CECT, where a pseudocyst and WON can be difficult to
distinguish. Imaging by MR or EUS can better delineate the solid
components within a collection.

In the absence of a specific diagnostic marker of pancreatic necrosis, many
serum predictors have been proposed. An ideal predictor or prognostic indicator should be simple, cheap, reproducible, valid, available on admission, and specific for necrosis. While a full discussion of markers is beyond the scope of this chapter, there are several that fulfill most of these criteria, compare favorably with CT scanning, and have an established role in routine clinical practice.

C-reactive protein (CRP) is the most widely used predictor of pancreatic necrosis and is also useful as a daily monitor of disease progress. The accuracy in predicting the presence of necrosis is about 85%, but it requires 3 to 4 days after the onset of the disease to reach this level. The threshold values depend on the assay and the study used. A commonly used threshold is greater than 120 mg/L. Other prognostic markers, none of which has been shown to outperform CRP, include interleukin-6 (IL-6) (threshold >14 pg/mL) which peaks a day earlier than CRP; polymorphonuclear elastase (threshold >120 µg/L), which peaks early and reflects neutrophil activation and degranulation; and phospholipase A2 type II (threshold >15 U/L). Urinary trypsinogen-activating peptide has also been proposed as a predictor of necrosis, but is not the major advance that was first anticipated. Procalcitonin has been proposed as a sensitive and specific marker for infected necrosis but it has not become part of routine management.

The diagnosis of infected necrosis is very important because it is generally considered an indication for intervention. Rarely, the early invasion of gas-forming organisms, such as Clostridium perfringens, makes the diagnosis of infection on CT scanning straightforward. It is more usual to suspect pancreatic infection with rapidly progressive disease or a secondary deterioration after 2 or 3 weeks of admission. This is often heralded by a significant rise in CRP. A CECT scan will usually confirm the presence of a tense collection with rim enhancement arising from the region(s) of pancreatic necrosis. The presence of gas within the tissues confirms infection, with an “air bubble” appearance (Fig. 69-1), but this is present in the minority of cases.

Clinical practice guidelines are consistent in their recommendation to use FNA as the gold standard test to diagnose infected necrosis. It is true that infected ANC and WON are most accurately diagnosed by image-guided (CT or ultrasound) FNA for Gram staining and/or bacterial culture. Suspicion of infection is raised with a significant and secondary clinical deterioration and
the associated rise in serum markers (eg, CRP, procalcitonin) which makes the diagnosis of infection highly probable. Certainly there is usually enough suspicion to proceed with antibiotics, CECT, and percutaneous or endoscopic drainage, which allows bacterial cultures. There has been some concern that FNA is associated with a potential risk of secondary infection. In summary, it is better to consider FNA of ANC or WON as an adjunctive measure and one that is only undertaken in a patient in whom there is already a strong clinical suspicion of infection and in whom confirmation of infection will directly result in intervention.

**INDICATIONS FOR INTERVENTION**

The decision to directly intervene to treat complicated acute pancreatitis is one of the most difficult decisions in clinical practice. Intervention is defined as invasive treatments (radiologic, endoscopic, surgical) beyond medical, nutritional, and intensive care management. The primary indication for intervention is the development of infected necrosis (in ANC or WON) in conjunction with clinical deterioration, but it is no longer considered an absolute indication for intervention in many centers. Other indications for further intervention are the failure of radiologic or endoscopic drainage, where there is evidence of persistent sepsis, and organ dysfunction. The indications for intervention in the absence of infection are very limited. A rare indication for intervention, irrespective of the infection status of the necrosis, is the development of massive hemorrhage or bowel perforation (eg, colon or duodenum). Intervention on patients with sterile necrosis is no longer advocated unless there is acute clinical deterioration despite maximal supportive care and there is a well-defined target lesion to drain or debride. Intervention is also occasionally required in those patients with sterile necrosis who “fail to thrive” and are unable to be discharged. These patients often have abdominal symptoms and intolerance to oral feeding after a month or more. The vast majority of patients with sterile necrosis can and should be managed without surgery.

**TIMING OF INTERVENTION**

Historically, surgical intervention for pancreatic necrosis was performed during the first week after disease onset. Early surgery was advocated in
order to remove the dead tissue, the focus of infection, and terminate the inflammatory process. We now know that the inflammatory cascades are not easily switched off, and are exacerbated by the surgical procedure. Early surgery is more difficult and dangerous because the necrotic tissue is immature, poorly demarcated, and not easily separated from viable tissue, resulting in a significant risk of bleeding. In addition, early surgery may cause infection of sterile necrosis. With mortality rates of up to 65%, the trend toward early intervention has been curtailed, and intervention has become progressively later. The current concept for timing of intervention is that it should be undertaken as late as possible after disease onset (preferably 3-4 weeks), when the necrotic process has stopped extending, when there is clear demarcation between viable and nonviable tissues, and when infected necrotic tissue has become organized and “walled off.” Importantly, this delay allows time for stabilization of the patient through intensive care support, reduces the risk of new-onset organ dysfunction attributable to the intervention, and decreases the risk of bleeding and pancreatic insufficiency through the unnecessary removal of viable tissue.

This delay to debridement, by whatever means, is enabled by the adoption of the step-up approach (see later) that recommends radiological or endoscopic drainage first and then supportive measures. The concept of “drain first” should include efforts to optimize drainage by up-sizing, flushing, irrigation, replacement, and additional drains, as required. Prior drainage often results in an improvement in the patient’s overall clinical status. The type and timing of further intervention is dictated by a number of factors, including the patient’s condition and comorbidities, local expertise, and the anatomical location and complexity of the lesion. This decision is best made in a high-volume center with experience and expertise to ensure the timing and type of intervention is optimal.

**TYPES OF INTERVENTION**

There are many different interventions, and the challenge is to select the intervention appropriate for the particular local complication, taking into account the anatomical location, infection status and complexity of the target lesion(s), the physiological status, comorbidity of an individual patient, and the availability of expertise with the type of intervention. A review of current guidelines highlights the absence of level 1 evidence to guide decision
making regarding the types of intervention. There have been two broad philosophies regarding the type of intervention used. Some experts state that open surgical drainage and necrosectomy remains the gold standard in the management of infected pancreatic necrosis, and reserve less invasive interventions for subsequent complications. These include percutaneous and endoscopic drainage of residual fluid complications. Such a step-down approach contrasts with the step-up approach, which advocates the use of less invasive interventions initially (eg, percutaneous or endoscopic drainage), and then stepping up to minimally invasive surgical interventions and only employing open surgical techniques later in the disease course in those who fail to respond. These two approaches have been subjected to a randomized controlled trial in the PANTER trial. This demonstrated that the step-up approach reduced the rate of the composite endpoint of major complications and/or death. Mortality itself was not decreased, but new-onset multiple organ failure occurred less often in patients assigned to the step-up approach. Another important finding was that a third of patients who would have previously undergone an open necrosectomy were managed by drainage alone.

There is a need to standardize the description of invasive interventions to facilitate communication between clinicians, comparison of techniques, and controlled clinical trials. The VRP classification is based on the method used to Visualize the lesion, the anatomical Route taken to reach the lesion, and the Purpose of the intervention.

- The various ways to visualize the target lesion include open procedures (where the operative site is exposed through the skin incision), endoscopic procedures (where the operative site is visualized with an endoscope (eg, gastroscope, laparoscope, or nephroscope), radiological procedures (where CT, ultrasound, or fluoroscopy are used to visualize the lesion during the procedure), and hybrid procedures that combine endoscopic and radiological techniques.
- The different routes taken by reach the target lesion include the external route into the body (skin or external orifice) and the internal route to reach the target lesion (through the gastrointestinal wall, peritoneum, or retroperitoneum) (Fig. 69-10).
The overall purpose of treatment is to drain fluid and remove areas of necrotic and infected tissue. However, the way in which this is achieved varies considerably, with some procedures being considerably more aggressive than others. Therefore, the purpose of individual interventions may be to effect simple drainage alone, lavage of the necrotic cavity to assist drainage of necrotic debris, fragmentation of necrotic tissue to facilitate its drainage, débridement of necrotic tissue, and excision or resection of the pancreas. Drainage procedures involve allowing fluid and solid necrotic to drain externally out of the body or internally into the gastrointestinal tract. Lavage describes flushing away solid necrotic matter with fluid to facilitate external or internal drainage. Fragmentation is a method used to break down solid necrotic matter by instrumental or mechanical disruption to facilitate drainage. Débridement, which is often termed “necrosectomy,” involves removing solid necrotic matter (typically with blunt dissection), and may or may not include postoperative lavage. Débridement may involve removal of all or only some of the necrotic tissue, although normal tissue is not intentionally removed. Only during excision or resection of the pancreas is normal tissue intentionally removed.
removed along with devitalized tissue. Such an approach is no longer recommended.

THE “STEP-UP APPROACH” TO INTERVENTION

There have been significant changes in the approach to intervention in recent years. The focus shifted from resection to debridement decades ago, and we are now in the process of shifting the emphasis from debridement to drainage. Complete debridement is no longer considered essential; rather, sufficient debridement of necrotic tissue should be achieved to optimize drainage.

Figure 69-11 is an algorithm for clinicians who are faced with the management of patients with infected necrosis (ANC or WON). In general, when patients deteriorate despite maximum intensive care, the intention is now to institute or optimize drainage (endoscopic or radiologic). If the patient does not show any improvement over 48 to 72 hours, then the intervention is intensified. This might entail insertion of further drains. Endoscopically, this would often mean the insertion of a self-expanding metal stent (see above) through which endoscopic debridement can be undertaken. Alternatively, a percutaneous track can be dilated or a small flank incision made to allow for minimally invasive surgical debridement using a nephroscope or laparoscope. When these approaches fail, and only then, open surgical debridement is considered.
The target lesion is best delineated by CECT or MRI scanning, noting the size, wall maturity, extent, complexity, and anatomical relationships. In addition, it is used to determine whether there is safe access to the lesion, and which route (Fig. 69-11) and which method (radiologic or endoscopic) is preferred for drainage.

**RADIOLOGIC INTERVENTION**

The purpose of radiological techniques is to drain (with or without lavage) and to provide an aid to access for minimally invasive debridement (see below). Percutaneous catheter drainage can be used as a primary treatment for infected ANC/WON and more definitive treatment be delayed until the patient has clinically stabilized and wall-matured, or as a secondary...
treatment for residual collections. Further, percutaneous drainage is the sole treatment in about half the patients. Most collections are located in the lesser sac, anterior pararenal space, into the root of the small bowel mesentery and the paracolic gutters. The usual internal routes to the target lesion are retroperitoneal or transperitoneal. Less commonly, transgastric, transduodenal, and transhepatic routes used. While transgressing the stomach poses little infection risk, gastric peristalsis may dislodge the catheter over time. Transgressing the liver carries the risk of bleeding, but in practice is generally safe. Routes should avoid colon, small bowel, spleen, and kidney to minimize the risk of hemorrhage and bacterial contamination. A retroperitoneal approach that avoids the peritoneal cavity is the preferred route, as this prevents contamination of the peritoneal cavity and possible peritonitis.

Typically percutaneous catheters have multiple side holes and a minimum diameter of 12 to 14 Fr (4.0-4.7 mm). Sometimes multiple catheters are required, for large or complex lesions. Lavage can be employed to reduce the concentration of digestive enzymes and proinflammatory mediators in the lesion, help maintain patency, and to assist the removal of solid necrotic debris from the cavity. There have been unsubstantiated concerns that lavage might spread infection, either from infected fluid spilling over into previously sterile cavities or from the increased intracavity pressure resulting in translocation of bacteria into portal circulation.

The efficacy of drainage procedures is limited by the contents of the target lesion. Success with predominantly solid lesions is rare. In patients with pancreatic necrosis treated with percutaneous catheter drainage, approximately half will be successful and not require surgical intervention. Failure of catheter drainage includes persistent systemic or local manifestation of infected necrosis, physiological deterioration despite drain patency, persistent abdominal pain, and intolerance of oral intake after the systemic inflammatory response syndrome has resolved. In some specialized centers, interventional radiologists have attempted debridement, through the use of snares, baskets, or by applying suction to a catheter during its removal.

ENDOSCOPIC INTERVENTION
Peroral flexible endoscopic techniques follow an internal route through either the gastric or duodenal wall or duodenal papilla, and some authors consider this to be a form of natural orifice transluminal endoscopic surgery (NOTES). Initial descriptions of flexible endoscopic treatment of pancreatic necrosis used lavage and drainage without instrument-guided débridement. A more aggressive approach was subsequently introduced, which demonstrated necrotic tissue could be debrided with baskets, snares, forceps, and suction. ERCP may be used to diagnose any communication between the duct and cavity or duct stenosis or disruption, and transpapillary stenting can be employed to decompress the duct. Puncture of the posterior gastric wall into the target lesion is performed at the point of maximal bulging, although confirmation of the location with EUS helps achieve safe deployment to avoid injury to vessels. The injection of contrast with fluoroscopy can be used to determine the extent of the cavity. The gastric insertion site is balloon-dilated. For lavage and drainage, a 7 Fr nasocystic (lavage) and a 10 Fr pigtail drain (drainage) are placed in the cavity. Necrosectomy may be performed with endoscopic instruments (eg, Dormia basket or polypectomy snare), and introduction of a forward-viewing endoscope into the necrotic cavity can be used for better visualization during the necrosectomy (Fig. 69-12). Multiple necrosectomy procedures are usually required to clear the cavity of necrotic tissue.
FIGURE 69-12 Cross-sectional views depicting video-assisted debridement of infected of “walled off necrosis” (A) and endoscopic transgastric drainage and necrosectomy (B).

The introduction of transgastric self-expanding metal stents (SEMS) has been a significant advance in the endoscopic treatment of infected ANC and WON. These stents are designed with a wide lumen (eg, 2.5 cm), wide flanges (to prevent migration) and even wall-apposing features (to reduce the risk of leakage) (Fig. 69-9). This facilitates direct endoscopic debridement, but it has been noticed that this is less often required with the wide lumen stents, possibly because of the liquefying action of gastric juice on the necrotic tissue.

Flexible endoscopic debridement has also been used percutaneously (“sinus tract endoscopy”). A similar technique has been described following open necrosectomy through a translumbar incision, where a flexible endoscope is inserted into the cavity for débridement. Another endoscopic approach is to debride through a percutaneous endoscopic gastrostomy (PEG). Usually multiple débridement procedures are required
because of the inefficiency of extraction. The wide range of endoscopic approaches to necrosectomy and the absence of formal comparison make a recommendation for the optimal approach difficult. The selection of an endoscopic technique will be influenced by training, experience, and availability of equipment.

MINIMALLY INVASIVE SURGICAL INTERVENTION

Over the last decade, a wide range of endoscopic surgical approaches for pancreatic necrosectomy have been described, including infracolic laparoscopy, transgastric laparoscopy, hand-assisted laparoscopy, retroperitoneal laparoscopy, and retroperitoneal nephroscopy.\textsuperscript{78-82} While some endoscopic procedures do not use radiologic imaging, many are hybrid procedures using fluoroscopy or EUS. This array of minimally invasive techniques can be classified by the type of scope used.\textsuperscript{83}

**Laparoscopic Techniques.** In 1996, Gagner described the first true endoscopic treatment of necrotizing pancreatitis, where the pancreas was debrided using a laparoscopic approach.\textsuperscript{84} Most laparoscopic techniques are minimally invasive versions of open surgical techniques, and use either an anterior or lateral approach (see below). In Gagner’s original description of laparoscopic necrosectomy, two anterior routes (retrogastric retrocolic and transgastric) and one lateral route were described.\textsuperscript{84} This technique has been modified. Of the lateral approaches, one of the most widely used laparoscopic techniques is videoscopic-assisted retroperitoneal débridement (VARD) (Fig. 69-12).\textsuperscript{82,61} In this technique, prior percutaneous drainage is followed by a 4- to 6-cm incision in the left flank using the drain as a guide. A finger is used to probe and confirm entry into the necrotic cavity. Fluid and loose necrotic debris are removed by suction. Using right-angled retractors, the laparoscope is inserted along with the irrigating catheter (to aid visualization) and further debridement is achieved under direct vision with the gentle use of sponge forceps. The incision can be sealed with wet sponges and towel clips to allow better visualization by insufflation with CO\textsubscript{2}. The objective is not to achieve complete debridement but optimal drainage. Large bore drains (eg, 28-32 Fr Protex chest drains) are brought out through the flank incision. These drains are used for drainage and lavage. An ostomy bag can be positioned over the flank incision between lavage sessions.
The first randomized controlled trial comparing two different minimally invasive approaches to the treatment of infected pancreatic necrosis has now been published. In this pilot study ("PENGUIN"), endoscopic transgastric necrosectomy was found to be superior to the VARD procedure. There was a reduction in the incidence of the predefined composite endpoint (new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, and/or pancreatic fistula) or death. There was a decrease in the incidence of new onset of multiple organ failure, supported by the finding that there was a significantly lower proinflammatory response after the procedure, and a reduction in the incidence of pancreatic fistulation.

Nephroscopic Techniques. The use of a nephroscope for necrosectomy was termed “percutaneous necrosectomy” by the unit that pioneered this approach. The purpose is to debride necrotic tissue and establish continuous lavage. The rigid nephroscope has an irrigating channel that provides superior visualization to laparoscopic techniques. The limitation is the working channel, which limits the amount of debridement. The first step is to insert a drainage catheter under CT guidance into the pancreatic lesion. The preferred path for drainage is between the lower pole of the spleen and the splenic flexure, although in right-sided necrosis a path through the gastrocolic omentum (anterior to the duodenum) may be necessary. The patient is then transferred to the operating room and positioned in the appropriate lateral position. The drain tract is then dilated to allow insertion of a 34 Fr Amplatz sheath. The nephroscope is inserted through the sheath into the cavity, and lavage is used to clear away pus and debris. Following necrosectomy, a 32 Fr soft drainage tube is left in the cavity. An additional catheter may be used to allow continuous postoperative lavage. Repeat procedures are often required after 2 to 10 days.

OPEN SURGICAL INTERVENTION

The role of open surgical treatment of infected pancreatic necrosis is diminishing with the accumulating evidence for the less invasive approaches. It is now reserved for those who fail minimally invasive intervention and for when a laparotomy is required for additional reasons, such as abdominal compartment syndrome and intestinal infarction/perforation. Prior CECT scanning will allow determination of the extent of the target lesion and allow
formulation of the operative plan. The abdomen is best entered though a bilateral subcostal incision since this allows better access to the extremities of the gland and less contamination of the greater peritoneal sac if there are subsequent procedures. The pancreas is exposed by dividing the gastrocolic omentum (Fig. 69-11) or gastrohepatic omentum to access the pancreas through the lesser sac. The body and tail of the pancreas can be exposed by elevating the transverse colon and gaining access to the lesser sac via the transverse mesocolon (Fig. 69-12). Inflammatory adhesions may exist between the pancreas and stomach or transverse mesocolon, and great care is required during exposure. It is generally useful to take down both the hepatic and splenic flexures if possible, as this will facilitate exposure and reduce the risk of colonic fistula secondary to drain erosion. When the process involves the head of the pancreas, access might require medial mobilization of the duodenum.

The plan is to drain all fluid collections, debride all devitalized tissue, and avoid hemorrhage and enteric fistulation. Infected necrotic tissue and fluid are sent for bacterial culture to confirm the causative organisms and rationalize antibiotic therapy. Débridement of necrotic tissue is performed bluntly, usually with digital dissection, careful use of instruments, and lavage. Only loosely adherent necrotic tissue should be removed, and this is easier if there has been a significant delay between onset of disease and surgery. Use of a systematic approach, such as examining in turn the retroperitoneum behind the transverse, ascending, and descending colon, helps to ensure all areas of necrotic tissue are identified and removed. If multiple procedures are planned, the first necrosectomy provides the best exposure, and therefore the most complete débridement that is safe should be accomplished at this time. The thoroughness of the initial débridement is the most important factor in determining the need for subsequent reoperation. The need for complete débridement has been questioned, and the risks of aggressive débridement have been balanced against the risks of persisting sepsis.

A key point is to avoid sharp dissection in order to prevent major hemorrhage. Adherent necrotic tissue should be left in situ, as this will subsequently demarcate and become loose. Strands of tissue forming bridges across the cavity may be vessels and should not be avulsed. This is important, because bleeding from inflamed vessels within the retroperitoneum is difficult to control and may require formal packing.
Following débridement, extensive irrigation is used to flush away necrotic debris, inflammatory exudates, and residual bacteria. Postoperative lavage may be employed, and this can be either intermittent or continuous (Fig. 69-11). The fluids most commonly used for this purpose are normal saline or peritoneal dialysis fluid, although there is no evidence to support the best fluid or flow rate.

The choice of open surgical procedure is determined by the location, extent, and maturity of the necrotic material; status of the infection; the patient’s condition; the degree of organ dysfunction; and the preference and experience of the surgeon. A number of different approaches have been described (Table 69-4), some of which are only of historical interest. Interventions are complex, fraught with potentially life-threatening complications, and should only be performed by experienced surgeons in regional centers.

There are several approaches to open necrosectomy, and there is no high-level evidence to support one over the other. While the débridement technique for all the approaches is similar, they differ in terms of how they provide egress for infected fluid, debris, and tissue.

**Open necrosectomy with Closed Packing.** The goal of necrosectomy with closed packing is to perform a single operation, with thorough débridement and removal of necrotic and infected tissue, and to avoid or minimize the need for reoperation or subsequent drainage. Some units use gauze-stuffed Penrose drains placed via separate stab incisions, but there are many variations in practice with regard to the type and number of drains. With the Penrose drain technique, the intention is to fill the cavity and provide compression rather than facilitate external drainage per se, and between two and twelve drains are usually placed. Additional silicon drains (eg, Jackson-Pratt) are placed in the pancreatic bed and lesser sac to drain fluid from the area. Primary closure of the abdomen is routine with this approach. The stuffed Penrose drains are removed once every other day, starting 5 to 7 days postoperatively. The silicone drains are removed last.

**Open Necrosectomy with Open Packing.** The difference between this approach and closed packing is that the abdomen is left open after débridement and packing of the abdomen. An alternative form of open packing uses a 20-cm flank incision instead of an anterior laparotomy.
Open packing techniques have been reported to have higher incidences of fistulae, bleeding, and incisional hernias, as well as a slightly higher mortality rate. However, it should be noted there are no prospective trials comparing open packing with any other techniques.

**Open Necrosectomy with Continuous Closed Postoperative Lavage.** In this technique, débridement is followed by continuous peripancreatic lavage to remove infected necrotic debris, peripancreatic exudates, and extravasated pancreatic exocrine fluid. Drainage catheters, usually two on each side, are placed with their tips at the head and tail of the pancreas behind the ascending and descending colon. Placement of sump drains (20-24 Fr) with two lumens allows inflow of lavage fluid and outflow of drainage fluid. Larger silicon drains (28-32 Fr) allow evacuation of larger necrotic debris. During closure, a closed peripancreatic compartment is attempted by resuturing the gastrocolic and duodenocolic ligaments. Postoperative continuous lavage is instituted at 1 to 10 L per day, and is usually continued until the effluent is clear and the patient shows improvement in clinical and laboratory parameters. There is no evidence to support the best irrigation fluid, the optimal number or caliber of drains, or the duration of irrigation.

**Programmed Open Necrosectomy.** The principle of this approach is to be more conservative with débridement, particularly if the necrosis has not fully demarcated, with the intention of performing repeat procedures until débridement is no longer required. Following necrosectomy, the pancreatic bed is packed and drains are placed on top of the packing. The abdominal wall is closed with a zipper or mesh sewn to the fascia. This allows easy repeated access to the abdomen and helps to prevent wound retraction. Reoperation is repeated every 48 hours until there is no further necrotic tissue to remove. In a proportion of patients, primary closure is not possible and healing by secondary intention is allowed to occur. This procedure may be modified with the addition of intra-abdominal vacuum sealing (negative pressure 50-75 mm Hg) in order to encourage granulation of the pancreatic bed.

**REGIONAL COMPLICATIONS**
Vascular Complications

VENOUS THROMBOSIS

Thrombosis of the splenic vein is a rare complication of acute pancreatitis and one that usually develops a few weeks after the onset. The etiology is multifactorial, but extrinsic compression of the vein by the swollen pancreas and/or fluid collection is important. Other factors include hypercoagulability and hemoconcentration. The consequences of splenic vein thrombosis are splenomegaly with discomfort and possible hypersplenism. Segmental venous hypertension may result in upper gastrointestinal bleeding from gastric varices. Because the risk of gastric variceal bleeding from pancreatitis-induced splenic vein thrombosis is low (5% for CT-identified varices and 18% for endoscopically identified varices) routine splenectomy is no longer recommended. Portal vein thrombosis occurs insidiously, may be identified on CECT, and may be discovered after gastrointestinal hemorrhage has occurred. The consequences of acute superior mesenteric vein thrombosis are venous ischemia and infarction of the intestine. CECT scanning is helpful in the diagnosis of venous thrombosis and may show features of impaired mucosal enhancement, edematous swelling of the vessel wall, and most commonly, filling defects within the vein. The role of acute anticoagulation is controversial because of the risk of bleeding. If thrombosis occurs later in the disease course, anticoagulation can be prescribed with less trepidation. Thrombolytic therapy and surgical thrombectomy have no established role in the context of acute pancreatitis. Acute venous thrombosis is associated with a 25% recurrence rate without anticoagulant therapy and a 30% mortality. Anticoagulant therapy combined with surgery is associated with the lowest recurrence rate (3%-5%).

BLEEDING

Bleeding associated with severe acute pancreatitis is usually, but not always, due to a pseudoaneurysm related to a pancreatic pseudocyst. The splenic artery is the most commonly affected artery (30%-50%) because of its proximity to the pancreas, followed by the gastroduodenal artery (10%-15%), the inferior and superior pancreaticoduodenal arteries (10%), and all others to a lesser extent.
Pathogenesis. The disruption of the pancreas by necrosis and the damage to pancreatic ducts leads to the accumulation of activated proteolytic enzymes (eg, elastase), weakens the vessel wall, and promotes aneurysmal dilatation. This process is accelerated in the presence of infection.

Diagnosis. Patients usually present with hypovolemic shock or with an unexplained drop in hemoglobin concentration. Bleeding may occur into a pseudocyst and tamponade, preventing any overt evidence of bleeding. Very rarely the diagnosis will be made in a patient with a known pseudocyst who develops an abdominal bruit.

Selective mesenteric angiography is the best way to make the diagnosis of pseudoaneurysm (Fig. 69-4), although it can often be detected on the arterial phase of CT scan, which is frequently used as a screening test in a stable patient. Angiography usually accurately identifies the location of the pseudoaneurysm and its relationship to named vessels.

Treatment. Pancreatic or peripancreatic bleeding is one of the most formidable and life-threatening complications of acute pancreatitis. The standard of care is angioembolization, with surgery only required in patients who have failed this approach or who are not stable enough to be managed in the interventional radiology suite. Success with embolization is operator-dependent, but approaches 90% in leading centers. Failure results from an inability to selectively cannulate the bleeding vessel, or poor placement of embolization material. Recurrent bleeding occurs in fewer than 40% of patients, and the overall mortality is under 20%.

If emergency laparotomy is required for bleeding, it may not be possible to arrange prior angioembolization. The lifesaving surgery may involve under-running the bleeding vessel (inside or outside the pseudocyst) and/or pancreatic resection. The mortality rate following surgical treatment of arterial hemorrhage during the acute phase of pancreatitis ranges from 28% to 56%, and is higher when bleeding is from the head of the pancreas. The mortality rate following surgical treatment of massive hemorrhage is usually over 50%.

Intestinal Complications

PARALYTIC ILEUS
The proximity of the inflamed pancreas to the root of the small bowel mesentery commonly results in regional self-limiting paralytic ileus affecting the duodenum, proximal jejunum, or transverse colon. Another factor that may contribute to the ileus is the relative splanchnic ischemia secondary to the reflex vasoconstriction in response to systemic hypotension, early in the disease course. An ileus gives rise to the classic “sentinel loop” and “colon cutoff” signs on plain abdominal radiographs.

**INTESTINAL ISCHEMIA AND NECROSIS**

Subclinical mucosal ischemia is common in acute pancreatitis, particularly during the early phase, and occurs in response to hypovolemia and reflex splanchnic vasoconstriction. Intestinal ischemia might be compounded by abdominal compartment syndrome, nonselective inotropes, and the demands of early and continuous enteral feeding. These are risk factors for nonocclusive mesenteric ischemia. Full-thickness necrosis is rare and probably involves venous and/or arterial thrombosis at sites proximal to the inflammatory process. The middle mesocolic vessels and the transverse colon are most at risk.

**INTESTINAL OBSTRUCTION**

Mechanical obstruction rarely complicates acute pancreatitis. The mechanism is usually inflammatory stenosis, which presents very late. It is unusual to require surgery.

**CHOLESTASIS**

Biochemical and clinical jaundice occur in less than 20% of patients with acute pancreatitis. The early identification of concomitant cholangitis is important and will require early ERCP and duct decompression. Cholestasis may be due to common bile duct stones or extrahepatic bile duct compression by a peripancreatic fluid collection. Long-term total parenteral nutrition will contribute to cholestatic liver dysfunction.

**SYSTEMIC COMPLICATIONS**
Systemic Inflammatory Response Syndrome

The systemic inflammatory response syndrome (SIRS) is common with acute pancreatitis and encompasses the hallmarks of a proinflammatory state (ie, tachycardia, tachynea or hyperpnea, hypotension, hypoperfusion, oliguria, leukocytosis or leukopenia, pyrexia or hypothermia, and the need for volume infusion) but without end-organ damage, identifiable bacteremia, or the need for pharmacologic support. SIRS is distinct from sepsis (where there is an identified pathogen) and septic shock (where there is associated hypotension). SIRS is best regarded as an exuberant host inflammatory response and the consequence of hypoperfusion.

There is no single trigger for SIRS. Instead, it represents a whole-organism response to a variety of quite different challenges. Theories on the drivers for SIRS include the immunologic dissonance theory (where there is imbalance between the pro- and anti-inflammatory responses) and the gut motor theory (where decreased intestinal perfusion and subsequent damage to the mucosal and immunologic barriers may allow the translocation of endogenous bacteria or their products into the systemic circulation). More recently, the intestinal mucosa has been considered another source of inflammatory mediators activated by hypoperfused mucosa. Measurement of intramucosal pH (tonometry) can stratify mortality risk in acute pancreatitis.

The mediation of SIRS is due to a number of well-described cytokines responsible for the proinflammatory state, a full description of which is beyond the scope of this chapter. In many patients with acute pancreatitis, SIRS progresses to multiple organ dysfunction syndrome (MODS) and possible end-organ damage. Occasionally, patients will be admitted with fulminant or early severe acute pancreatitis, often with respiratory and renal impairment from the outset, and these patients are responsible for early deaths. Organ failure on admission, which occurs in 30% to 40% of patients with necrotizing pancreatitis, is a very poor prognostic sign, doubling intensive care stay and increasing the mortality rate fourfold. Early aggressive volume resuscitation has an important role in attenuating the systemic inflammatory response.

Multiple Organ Dysfunction Syndrome
The development of MODS is common in severe acute pancreatitis. The most commonly affected organ systems are cardiovascular, respiratory, and renal. It has been defined as the presence of altered organ function in a severely ill patient such that homeostasis cannot be maintained without intervention. Many patients with early organ failure respond rapidly to supportive treatment and appear to have an otherwise uncomplicated outcome. These patients are said to have transient organ dysfunction, if it resolves within 48 hours. Patients with persistence and progression of early organ failure have a mortality rate in excess of 50%. It has been shown that organ dysfunction in the first week of admission is a dynamic process and the response to the initial intensive care is an important determinant of outcome.

Many potential early predictors of organ failure have been investigated. MODS can be predicted with reasonably high accuracy at the time of hospital admission using a combination of the anti-inflammatory cytokine IL-10 (an early marker of systemic inflammation) and serum calcium (an early marker of organ dysfunction).

There are many different MODS scoring systems, but the one recommended for acute pancreatitis is the modified Marshall score. The scoring systems do not tell the clinician when specific organ dysfunction is reversible or irreversible. Practically, a simple count of organs affected and the duration of the dysfunction will stratify mortality.

**Respiratory Complications**

Respiratory impairment can result from several causes, including atelectasis, pleural effusion, pneumonia, mediastinal pseudocyst or abscess, and/or adult respiratory distress syndrome (ARDS). Tachypnea, mild respiratory alkalosis, and mild hypoxemia are common within 2 days of the onset of acute pancreatitis. These clinical features usually can be corrected with analgesia, supplemental oxygen, and chest physiotherapy. A pleural effusion may require a chest drain. Impending respiratory failure is suggested when the arterial PO$_2$ remains less than 60 mm Hg despite high-flow oxygen by mask. These patients should be considered for mechanical ventilation. Lung-protection ventilation strategies, with low tidal volumes for patients with ARDS, are recommended. ARDS may occur within a few days of admission or after the development of infected necrosis and septicemia.
ARDS results from the release of activated pancreatic enzymes, vasoactive lysosomal enzymes, and especially phospholipase A2 (which destroys surfactant). Parenchymal injury appears to be due primarily to oxidative damage from the activated neutrophils in the lung.

Renal Complications. Renal impairment is usually due to both hypovolemia (prerenal failure) and direct nephrotoxicity from the inflammatory mediators of acute pancreatitis. Activation of the renin-angiotensin system may contribute to reduced renal perfusion. This manifests as oliguria (<30 mL/h) or anuria and as an increased serum concentration of creatinine and urea. The initial approach is adequate intravenous crystalloid administration to achieve a satisfactory urine output. Then diuretics (furosemide 20-200 mg/24 h) and dopamine infusion (4 µg/kg/min) should be considered. Further deterioration will necessitate continuous hemofiltration and/or hemodialysis.

Cardiovascular Complications. These include arrhythmias, pericardial effusion, impaired myocardial contractility, reduced peripheral vascular resistance, and increased permeability. Hypovolemia, from third-space fluid loss, is common during the first 12 hours and may be up to 30% of blood volume in severe acute pancreatitis. Circulatory failure (mean arterial pressure <70 mm Hg) requires prompt, aggressive fluid resuscitation and inotropic support. SIRS is characterized by decreased peripheral vascular resistance and is the reason for the preferred use of norepinephrine to increase vascular tone and blood pressure (dose 0.05-0.2 µg/kg/min). Epinephrine (dose 0.05-0.2 µg/kg/min) also may be used to support cardiac output. Unfortunately, these inotropes will compound splanchnic vasoconstriction because they are nonselective.

Metabolic Complications. Hypocalcemia is the most frequent metabolic disturbance, and it usually occurs during the first week. Low serum albumin will make the hypocalcemia appear worse, and therefore replacement should be based on ionized calcium. There are several factors likely to be responsible for low calcium. Primarily, calcium is sequestered in areas of fat necrosis by the process of saponification. In addition, there is probably a contribution from altered calcium-regulating hormones (eg, calcitonin, parathyroid hormone, and glucagon). Hypomagnesemia may inhibit parathyroid hormone and contribute to the hypocalcemia.
Hyperglycemia is a frequent finding and usually corrects without the need for treatment. There are three contributing factors to hyperglycemia, including a stress-induced increase in cortisol and catecholamines, hyperglucagonemia, and probably most important, an insulin deficiency that may reflect necrosis of the islet cells. Pre-diabetes and diabetes are common after acute pancreatitis, and occur in nearly 40% of patients after hospital discharge.\textsuperscript{102} It does not appear to be related to the severity of acute pancreatitis. Prevalence of newly diagnosed diabetes is much higher after acute pancreatitis (23%) than the prevalence of diabetes in the general population (4%-9%).

Disseminated intravascular coagulopathy is not common, but there is a well-recognized tendency toward hypercoagulability in acute pancreatitis. Other rare complications include subcutaneous fat necrosis and polyarthritis, which are also seen in patients with acinar cell carcinoma of the pancreas and thought to be due to increased serum lipase. There have also been reports of osteolysis and rhabdomyolysis in severe acute pancreatitis.

Pancreatic encephalopathy is a rare complication of acute pancreatitis. Clinical features include focal neurologic signs and acute onset of dementia. This picture can fluctuate over time, and cyclic progression with remission and relapses has been described. Although the exact mechanisms are unclear, postmortem examination reveals amylase in the cerebrospinal fluid. MRI of the brain may be helpful, as patchy white matter signal abnormalities resembling the plaques seen in multiple sclerosis may reflect the lesions that are found in the cerebral white matter of postmortem-confirmed cases. Treatment is supportive. Any patient with suspicious or unusual neurologic symptoms and signs associated with possible malnutrition, hyperemesis, or malabsorption should be given intravenous thiamine to avoid the potential morbidity and mortality associated with undiagnosed Wernicke encephalopathy.

Protein−calorie malnutrition is a complication of acute pancreatitis, especially when it is severe and associated with infected necrosis. These patients have a significantly elevated resting energy expenditure, and it has been shown that total parenteral nutrition is unable to reverse this hypercatabolic insult on body protein.\textsuperscript{103} This underlies the importance of sepsis control to achieve the full benefits of nutritional support, enteral or parenteral. A full discussion on nutritional support in patients with severe acute pancreatitis can be found in Chapter 54.
CONCLUSION

The many and varied complications of acute pancreatitis present a considerable clinical challenge and highlight the need for the treatment of patients with severe and critical acute pancreatitis to be in centers able to offer expertise in a wide range of disciplines including intensive care, surgery, endoscopy, radiology, infectious disease, and nutrition. The two primary goals of research in the field of acute pancreatitis should be aimed at preventing infected pancreatic necrosis and reducing the frequency and severity of multiple organ dysfunction. In the meantime, the clinician caring for patients with acute pancreatitis must remain vigilant to detect the development of local, regional, and systemic complications of this protean disease, and be well versed in the considerable recent progress in the treatment of local complications. This progress includes the more conservative approach to the simple pseudocyst, the step-up approach with the primary, and potentially sole, role of percutaneous drainage for infected local complications, and the evolution of minimally invasive techniques, which offer the opportunity for improved outcomes in patients with limited physiological reserve.

REFERENCES


INTRODUCTION

Acute pancreatitis is the most common gastrointestinal disease for which patients are acutely hospitalized, and its incidence continues to rise. The majority of patients (approximately 80%) with acute pancreatitis have mild disease, and symptoms usually resolve within 1 week with basic supportive care. The other 20% of patients develop a severe form of pancreatitis with organ failure and necrotizing pancreatitis. Necrotizing pancreatitis is now defined as either pancreatic parenchymal necrosis and peripancreatic fat necrosis or peripancreatic fat necrosis alone. The clinical course of these patients is often characterized by a persisting systemic inflammatory response syndrome and/or (multiple) organ failure for the first 1 to 2 weeks. Despite
maximal supportive care in the intensive care unit, mortality is up to 30% in patients with early persisting organ failure.\textsuperscript{5,6} Secondary infection of the necrosis develops in 30% of patients and carries a mortality risk of approximately 15%.\textsuperscript{7,8}

**CLASSIFICATION OF ACUTE PANCREATITIS**

A better understanding of local and systemic complications, together with better imaging and new interventions in acute pancreatitis, led to the Revised Atlanta Classification.\textsuperscript{2} This revised classification aims to clarify terminology and stimulate the use of uniform definitions and standardized reporting in patients with acute pancreatitis. Based on the absence or presence of local or systemic complications, 3 categories were defined in acute pancreatitis: mild, moderate, and severe (Table 70-1). Acute pancreatitis itself is divided into interstitial edematous pancreatitis and necrotizing pancreatitis, where local complications are linked to 1 of the 2 subtypes. Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (ie, sterile or infected), and walled-off necrosis (ie, sterile or infected) (Table 70-2).

**TABLE 70-1: CATEGORIES OF ACUTE PANCREATITIS AS DEFINED IN THE 2012 REVISED ATLANTA CLASSIFICATION**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient organ failure</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Persistent organ failure</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Exacerbation of preexisting comorbidity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Systemic complications:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient organ failure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Persistent organ failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation of preexisting comorbidity</td>
<td></td>
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</tbody>
</table>
The Revised Atlanta Classification is definitely a step forward in the classification of patients with acute pancreatitis. However, some practical issues with the classification need to be resolved. The cutoff value of 4 weeks is used for the definition of local complications. In the case of encapsulation of an acute necrotic collection, this is called walled-off necrosis after 4 weeks. The timing of encapsulation of collections, however, differs between patients and should probably be based on imaging instead of time from onset.

### TABLE 70-2: COLLECTIONS AS DEFINED IN THE 2012 REVISED ATLANTA CLASSIFICATION

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fluid collection (&lt;4 weeks</td>
<td>• Homogenous fluid density&lt;br&gt;• Confined by normal peripancreatic fascial planes&lt;br&gt;• No definable wall encapsulating the collection&lt;br&gt;• Adjacent to pancreas (not intrapancreatic)</td>
</tr>
<tr>
<td>after onset and edematous pancreatitis)</td>
<td></td>
</tr>
<tr>
<td>Pseudocyst (rare, usually &gt;4 weeks</td>
<td>• Well circumscribed, usually round/oval&lt;br&gt;• Homogenous fluid density&lt;br&gt;• Well-defined wall and completely encapsulated&lt;br&gt;• Adjacent to pancreas (not intrapancreatic)</td>
</tr>
<tr>
<td>after onset and edematous pancreatitis)</td>
<td></td>
</tr>
<tr>
<td>Acute necrotic collection (&lt;4 weeks</td>
<td>• Heterogeneous and nonliquid density&lt;br&gt;• No definable wall encapsulating the collection&lt;br&gt;• Location: intrapancreatic and/or extrapancreatic</td>
</tr>
<tr>
<td>after onset and necrotizing pancreatitis)</td>
<td></td>
</tr>
<tr>
<td>Walled-off necrosis (usually &gt;4 weeks</td>
<td>• Heterogeneous and nonliquid density&lt;br&gt;• Well-defined wall and completely encapsulated&lt;br&gt;• Location: intrapancreatic and/or extrapancreatic</td>
</tr>
<tr>
<td>after onset and necrotizing pancreatitis)</td>
<td></td>
</tr>
</tbody>
</table>
of disease.\textsuperscript{9} In acute pancreatitis, the most commonly used imaging modality is contrast-enhanced computed tomography (CECT). Determining the content of collections (ie, fluid and/or necrosis) can be difficult on CECT.\textsuperscript{9} Magnetic resonance imaging (MRI) is superior in this respect but is impractical in critically ill patients. These limitations of computed tomography (CT) can make implementation of the new classification difficult in some cases.

**PREDICTING SEVERITY**

To identify patients with a high risk for a severe course of their acute pancreatitis, prognostic scoring systems have been developed. There are several scoring systems, which are based on clinical and biochemical parameters (eg, the Ranson, Acute Physiology and Chronic Health Evaluation II [APACHE II], Imrie, or modified Glasgow scores). C-reactive protein and blood urea nitrogen are also often used in predicting severity during admission to the hospital. A systematic review on all these parameters showed that they have a high negative predictive value but low positive predictive value.\textsuperscript{10} CECT can assess morphologic abnormalities and can be used in scoring systems (eg, the CT severity index). However, CECT can underestimate morphologic abnormalities in acute pancreatitis in the first days of admission and is inferior to clinical scoring systems.\textsuperscript{2,11} A head-to-head comparison on the accuracy of scoring systems in predicting persisting organ failure showed that the modified Glasgow score served as best predictor.\textsuperscript{12} Still, more accurate markers are needed to predict the severity of acute pancreatitis.

Persistent organ failure is the key determinant for mortality in acute pancreatitis. Together with the lack of a strong marker to predict severity, the International Association of Pancreatology (IAP)/American Pancreatic Association (APA guidelines recommends that persistent systemic inflammatory response syndrome (>48 hours) be used as a marker to predict the severity of acute pancreatitis.\textsuperscript{3} Persistent organ failure is also used in the Revised Atlanta Classification to define the severity of acute pancreatitis (Table 70-1).

**EARLY SUPPORTIVE MEASURES**
Pain Management

Abdominal pain is the most dominant feature of acute pancreatitis during admission. Specific pain management in acute pancreatitis is lacking; therefore, the World Health Organization analgesic ladder should be followed during admission. Of course, proper pain management is crucial for all patients, but increasing evidence also suggests a beneficial impact of pain relief on both physiologic and immunologic response.

Fluid Therapy

Early in the onset of acute pancreatitis, there is often accumulation of fluid in the third space than can cause intravascular hypovolemia and might evoke or worsen organ failure. Extensive fluid resuscitation to correct or preferably prevent intravascular hypovolemia and maintain the microcirculation of the pancreas is therefore important in the supportive care during the first days of acute pancreatitis. More recent evidence also showed that uncontrolled, aggressive fluid therapy may induce morbidity and even mortality. For acute pancreatitis, there is a lack of quality evidence on which type of fluid therapy should be used. Results from a trial in patients with severe sepsis showed that when patients were resuscitated with hydroxyethyl starch (HES) there was an increased risk for death compared to Ringer’s lactate. The recent update of the IAP/APA treatment guidelines for acute pancreatitis recommends closely monitoring urine production and vital parameters and using Ringer’s lactate with an infusion rate of 5 to 10 mL/kg/h until resuscitation goals are reached.

Prevention of Infection

Prophylactic strategies should be focused on infections that occur early in acute pancreatitis and have a significant impact on mortality, especially bacteremia. It was hypothesized that administration of probiotics would be such a strategy. Before the PROPATRIA trial was performed, 2 smaller randomized, controlled, single-institution trials were conducted with probiotic prophylaxis in patients with severe acute pancreatitis. The first trial showed that
probiotics reduce pancreatic sepsis and the need for surgical intervention\textsuperscript{23}; the second study suggested that early nasojejunal feeding with synbiotics may prevent organ dysfunction in the late phase of severe acute pancreatitis.\textsuperscript{24} In the larger randomized controlled multicenter trial (PROPATRIA), probiotics were compared with placebo in patients with predicted severe pancreatitis. No effect was found on infectious complications, and increased rates of bowel ischemia (9\% vs 0\%) and mortality (16\% vs. 6\%) were present when compared to the placebo group.\textsuperscript{25} Although the mechanism of this adverse effect remains unknown, use of probiotics in acute pancreatitis is not recommended.

Studies in intensive care units showed that selective decontamination of the intestinal tract reduces mortality in general.\textsuperscript{26} Selective decontamination of the intestinal tract has also been performed in severe acute pancreatitis with beneficial results. However, no effect on mortality was found, and the design of the study was not optimal, with a lack of blinding and absence of a placebo.\textsuperscript{27} Potential benefits of selective decontamination of the intestinal tract should be weighed against an increase in antibiotic resistance and fungal colonization.\textsuperscript{28}

Several systematic reviews of randomized trials have shown that prophylactic administration of intravenous antibiotics does not prevent infected necrosis.\textsuperscript{29-31} Therefore, antibiotics in acute pancreatitis are only indicated when infections are proven or there is a high suspicion of infected necrosis.\textsuperscript{3}

**Nutrition**

When oral nutrition is not tolerated, enteral or parenteral nutrition should be administered. In severe pancreatitis, enteral nutrition is considered a therapeutic measure. Enteral nutrition through a nasoenteric feeding tube is superior to parenteral nutrition in terms of reducing organ failure, infected necrosis, and even mortality.\textsuperscript{32} These complications are thought to be caused by gut permeability, bacterial overgrowth, and bacterial translocation. Enteral nutrition is believed to stimulate intestinal motility and, with that, reduce bacterial overgrowth, which helps to conserve the gut mucosa.\textsuperscript{33,34} In the PYTHON trial, patients with predicted severe pancreatitis were randomized between early nasoenteric tube feeding within 24 hours of presentation to the
emergency department or an oral diet initiated 72 hours after presentation, with tube feeding only provided if the oral diet was not tolerated. The primary endpoint was a composite of major infection (infected pancreatic necrosis, bacteremia, or pneumonia) or death during the 6 months of follow-up. The main findings of the PYTHON trial were that routine early nasoenteral nutrition did not reduce the composite endpoint of infections or mortality. In the on-demand group, 69% of patients tolerated an oral diet and did not require tube feeding. Therefore, enteral nutrition is only recommended when an oral diet is not tolerated during the first 3 to 5 days of acute pancreatitis.

**Endoscopic Retrograde Cholangiopancreatography**

In the case of biliary pancreatitis and cholangitis, an urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy is indicated. There is no evidence that supports the use of ERCP in mild biliary pancreatitis in the absence of cholangitis or symptomatic common bile duct stones. It is hypothesized that performing an ERCP with endoscopic sphincterotomy in patients with predicted severe pancreatitis and without cholangitis may decrease the severity of the disease course. However, meta-analyses of randomized trials show conflicting results. The Dutch Pancreatitis Study Group is currently enrolling patients in a randomized multicenter trial to compare early ERCP with endoscopic sphincterotomy in patients with predicted severe pancreatitis without cholangitis (ISRCTN Registry No. ISRCTN97372133).

**MANAGEMENT OF INFECTED NECROSIS**

When patients fail to show clinical improvement from their systemic inflammatory response syndrome and/or organ failure or when they deteriorate during the course of the disease, infected necrosis should be suspected.

A CECT in these patients may show acute necrotic collection(s) or walled-off necrosis. Routine fine-needle aspiration (FNA) of peripancreatic collections to detect bacteria is not indicated because clinical signs and imaging signs are accurate predictors of infected necrosis in the majority of
patients. Pathognomonic for infected necrosis are gas bubbles in collections, which are caused by gas-forming bacteria or fistulas between the collection and the intestinal tract. FNA of the collection may be required when the diagnosis of infected necrosis is unclear. Still, one has to bear in mind that false-negative FNA results have been reported in 12% to 25% of patients and prospective studies with a proper design are lacking on this subject. If infected necrosis is suspected or proven, intravenous broad-spectrum antibiotics should be started, which subsequently can be narrowed down based on cultures of the infected collection. Full recovery with antibiotics has been described in some case series, but in the vast majority of patients, antibiotics should be regarded as supportive care during the disease course, while drainage and/or necrosectomy of (suspected) infected necrotic collections are regarded as definitive treatment.

Major surgery was traditionally performed early in the clinical course of necrotizing pancreatitis, but this practice has now been abandoned. When feasible, interventions are now postponed until walled-off necrosis is present on CECT, a process that usually takes 3 to 4 weeks. Delaying intervention until collections are completely encapsulated reduces morbidity and mortality when compared to early interventions in the first 2 weeks. Drainage of sterile collections carries a risk of introducing infection, thereby increasing the risk of morbidity and mortality. Therefore, in the acute phase, there is no indication for intervention in sterile collections. Several weeks after onset of the disease, in rare cases of obstruction of the biliary or gastrointestinal tract, long-lasting pain, or collections resulting from a disrupted pancreatic duct, sterile collections may be drained.

**INVASIVE TREATMENT**

Complete necrosectomy by laparotomy has long been the standard intervention in patients with necrotizing pancreatitis who showed clinical deterioration. Mortality (11%-39%) and morbidity (up to 95%) for this procedure were initially high. Due to better supportive care in the intensive care unit and optimal timing of surgery, recent studies have shown that the success rate of open necrosectomy has improved significantly (11%-19%).
Due to the introduction of minimally invasive techniques to drain and debride pancreatic necrosis (ie, catheter drainage and video-assisted retroperitoneal debridement), the indications for laparotomy have sharply diminished.\textsuperscript{42,46,47} Still, in the case of acute abdominal complications such as bowel ischemia, bowel perforation, and abdominal compartment syndrome, emergency laparotomy is required.\textsuperscript{7,48-50} During these laparotomies, it is recommended not to explore the retroperitoneum when infected necrosis is not present. The international guideline for abdominal compartment syndrome suggested drainage of ascites as a reasonable initial approach.\textsuperscript{51} However, this intervention should lead to rapid and sustained improvement of the patient’s condition.

**Minimally Invasive Interventions**

The first step of nearly all minimally invasive interventions is to drain the infected collections by a percutaneous catheter drain. If this drainage does not improve the clinical condition, drains may be revised, and if unsuccessful, necrosectomy of nonadherent necrotic tissue is performed. This approach causes less surgical injury and reduces the risk of iatrogenic damage and hemorrhage.

Several minimal invasive intervention strategies are available for drainage and/or debridement of infected necrotizing pancreatitis, such as percutaneous catheter drainage,\textsuperscript{52} percutaneous necrosectomy,\textsuperscript{53} video-assisted retroperitoneal debridement (VARD),\textsuperscript{54} laparoscopic necrosectomy,\textsuperscript{55} and endoscopic transluminal drainage and necrosectomy.\textsuperscript{56}

**Percutaneous Catheter Drainage and VARD**

To gain sepsis control in infected necrosis, a percutaneous catheter drain is used to drain “pus under pressure” in the necrotic collection and to serve as a bridge to definitive surgery. It is the least invasive procedure and is widely available. Success rates up to 50% (ie, no necrosectomy) have been described after percutaneous catheter drainage (Fig. 70-1).\textsuperscript{57,58}
FIGURE 70-1 Imaging of a patient with infected necrotizing pancreatitis. The patient recovered fully after a single large percutaneous drain was placed through the left retroperitoneum, without additional drainage procedures and without necrosectomy. Arrows point at the borders of the collection, with big arrowheads pointing at impacted gas bubbles and small arrowheads pointed at the gas-fluid level. (Reproduced with permission from van Brunschot S, Bakker OJ, Besselink MG, et al: Treatment of necrotizing pancreatitis, Clin Gastroenterol Hepatol 2012 Nov;10(11):1190-1201.)

Most of the peripancreatic collections can be reached percutaneously either via the retroperitoneal or transperitoneal route. When possible, the retroperitoneal route is preferred because it is associated with fewer complications and can be used as guidance for minimally invasive retroperitoneal necrosectomy (Fig. 70-2).
FIGURE 70-2 Percutaneous catheter drainage and video-assisted retroperitoneal debridement. **A.** Contrast-enhanced computed tomography (CT) image of a patient with necrotizing pancreatitis showing a transverse cross-sectional image. Catheter drainage through the left side of the retroperitoneum is the preferred route. **B.** Details on the drained area. **C.** Near the puncture site of the percutaneous drain, a small subcostal incision is made. The drain is used as a guide to the necrotic collection through the retroperitoneum. All visible necrosis is removed directly. **D.** Under vision of a 0-degree videoscope, further debridement is performed with laparoscopic instruments. (Reproduced with permission from van Brunschot S, Bakker OJ, Besselink MG, et al: Treatment of necrotizing pancreatitis, *Clin Gastroenterol Hepatol* 2012 Nov;10(11):1190-1201.)

In the PANTER trial, the minimal drain size was 12 Fr, and drains were irrigated 3 times daily with 250 mL of normal saline to keep the drains open. Additional drains can be placed or drains can be upsized to help to deal with inadequately drained collections. A VARD should always be preceded by percutaneous catheter drainage because a necrosectomy can be prevented in 35% to 50% of patients.
VARD is performed as follows. Under general anesthesia, in the right lateral position, a subcostal incision of a few centimeters is made near the exit of the drain. The drain is used, together with imaging, as a route through the retroperitoneum to the necrotic collection. Visible nonadherent necrosis is removed with grasping forceps from the collection. Under assistance of a 0-degree videoscope, loosely adherent necrosis is removed with long atraumatic graspers to reduce the risk of bleeding from viable underlying tissue. Finally, 2 large catheters are placed in the cavity for postoperative lavage (up to 10 L per 24 hours) exiting through stab incisions, and the fascia at the incision site is closed (Fig. 70-3).
FIGURE 70-3  Endoscopic transluminal drainage and endoscopic transluminal necrosectomy. A. Through the stomach wall, the necrotic collection is punctured and a guidewire is placed in the collection, if needed, under guidance of endoscopic ultrasound. Over the guidewire, the tract is balloon dilated. Two pigtail drains and a nasocystic catheter are placed into the collection for continuous lavage. B. Further dilation of the cystogastrostomy is performed, and the collection is entered by an endoscope. A necrosectomy can be performed under direct vision. (Reproduced with permission from van Brunschot S, Bakker OJ, Besselink MG, et al: Treatment of necrotizing pancreatitis, Clin Gastroenterol Hepatol 2012 Nov;10(11):1190-1201.)

The PANTER trial was a Dutch randomized multicenter trial that included patients with (suspected) infected necrotizing pancreatitis who were randomized between primary open necrosectomy (by laparotomy) or a surgical step-up approach that consisted of percutaneous catheter drainage first followed, if no improvement was present after 72 hours, by VARD.46 One-third of the patients in the trial were successfully treated with catheter drainage and reversal of sepsis after percutaneous catheter drainage occurred in the majority of patients. Also, due to the catheter drainage, a valuable time interval was created where the collections could become more encapsulated, facilitating the effectiveness of necrosectomy. The step-up approach showed a significantly lower rate of the combined endpoint of mortality and major complications compared to open necrosectomy (40% vs 69%). Some complications, such as pancreatic fistula formation (28% vs 38%), incisional hernia (7% vs 24%), and new-onset diabetes (16% vs 38%), were lower in the step-approach group when compared to the open necrosectomy group. Other complications, such as intra-abdominal bleeding (16% vs 22%) and enterocutaneous fistula or perforation of a visceral organ requiring intervention (14% vs 22%), did not differ significantly. Technical success in the step-up approach was high. Other retroperitoneal approaches are numerous (eg, single-port or multiport and flexible endoscopy access techniques).53,60-62

Endoscopic Drainage and Necrosectomy

Endoscopic transluminal catheter drainage followed, if needed, by endoscopic transluminal necrosectomy can be an alternative to the surgical
step-up approach and is gaining popularity.\textsuperscript{56,63,64} When the infected collection lies close to the duodenum or stomach, endoscopic transluminal drainage can be considered. Under deep sedation or general anesthesia, the patient is placed in the left lateral position. The size, content, and relation to other structures of the collection are examined by endoscopic ultrasound.\textsuperscript{65} Endoscopic drainage without ultrasound is possible, but the technical success is inferior to ultrasound-guided procedures.\textsuperscript{66,67} A 19-gauge FNA needle is used to access the collection through the duodenum or stomach. Cultures are taken, and under fluoroscopic guidance, a guidewire is introduced and looped into the collection.\textsuperscript{68} A larger fistula tract of up to 8 to 12 mm is created between the collection and the intestinal lumen by using electroscauterization and/or balloon dilatation. Two double pigtails and a nasocystic catheter are placed into the cavity and are used to flush the contents of the collection into the stomach (1 L per 24 hours). Alternatively, metal stents are used progressively as they have the advantage of creating and maintaining a larger opening (≥ 1 cm).\textsuperscript{69-71} The use of stents seems promising due to the ease of the endoscopic procedure and drainage of the cavity, but bleeding is a reported risk and this technique needs to be validated in randomized trials. Multiple collections can be drained by multiple cystogastrostomies or, alternatively, by combined percutaneous and endoscopic drainage.\textsuperscript{72-74}

If a patient does not improve within 72 hours after drainage, an endoscopic necrosectomy is performed. With a forward-viewing endoscope, the fistula tract is dilated up to 15 to 18 mm. The endoscope is advanced into the collection, and with endoscopic accessories (ie, snares, baskets, nets, and forceps), necrosectomy is performed through this tract, leaving the debris in the stomach. Finally, pigtails and a nasocystic catheter are left in the cavity to leave the fistula tract open.\textsuperscript{68,75,76} Until most necrotic material is removed, endoscopic necrosectomy is repeated every 48 hours.

The technical success of endoscopic drainage and necrosectomy is high and comparable with the surgical step-up approach, with clinical success rates up to 91%.\textsuperscript{65} Major complications were bleeding, spontaneous perforation of a hollow organ, and pancreatic fistula. Air embolisms have been described and hence CO\textsubscript{2} insufflation is recommended although this is not 100% protective since endoscopes insufflate without pressure control.
Which Technique Is Superior?

The method and route of drainage and/or necrosectomy depend largely on local experience available in the institution or region. Still, no definitive evidence exists as to what procedure should be the treatment of choice when necrosectomy is indicated. It is suggested that minimally invasive interventions are superior to open necrosectomy, although this has not yet been proven by well-designed trials. Head-to-head comparisons between all the different routes and techniques have not been performed. Even in the PANTER trial, VARD and open necrosectomy were not directly compared because VARD was always preceded by percutaneous drainage.46

Endoscopic transluminal necrosectomy was compared with VARD in a pilot study (the PENGUIN trial) in 22 patients with infected necrosis. The primary endpoint of the postoperative proinflammatory response and the combined endpoint of major complications and death were significantly reduced after endoscopic necrosectomy compared with VARD.77 The superiority of the less invasive endoscopic step-up approach over the surgical step-up approach in terms of clinical and economic outcomes should be confirmed in a large, multicenter, randomized controlled trial. The TENSION trial (ISRCTN Registry No. ISRCTN09186711) compares the endoscopic step-up approach with the surgical step-up approach regarding major morbidity and mortality and completed inclusion in February 2015.78

REFERENCES


INTRODUCTION

Chronic pancreatitis is an inflammatory and fibrosing disease of the exocrine pancreas characterized by irreversible morphological changes and permanent loss of function. The incidence of chronic pancreatitis has increased approximately fourfold over the past several decades. This apparent increase is due in part to a broadening of its definition and the inclusion of patients with earlier-stage disease. The natural history of chronic pancreatitis is unpredictable. Affected individuals typically suffer a pattern of persistent or recurrent attacks of pain and progressive pancreatic exocrine dysfunction. Additional symptoms may develop from extension peripancreatic inflammation and fibrosis to adjacent organs and vascular structures. In later stages, pancreatic endocrine insufficiency may develop. Decision making in the management of chronic pancreatitis must be individualized the specific anatomic and pathological circumstances, taking into account the extent of local expertise in various diagnostic and therapeutic modalities as well as the fact that there is a relative paucity of high-quality data on the clinical effectiveness of surgical and medical interventions. Optimal management is facilitated by a multidisciplinary approach that includes surgical, endoscopic,
and radiological expertise in addition to nutrition, endocrinology, pain management, and psychosocial support.

**DEFINITION AND RISK FACTORS**

Pancreatitis is thought to have its origin as an autodigestive disease initiated by inappropriate activation of pancreatic zymogens. The terms *acute pancreatitis* and *chronic pancreatitis* are often used to draw the temporal distinction between an isolated episode and a more persistent illness associated with a gradual, progressive loss of pancreatic function. In fact, pancreatitis represents a far more heterogeneous clinical entity than can be captured by these two simple descriptors. A number of international conferences have been held in order to develop uniform terminology to characterize the spectrum of morphology seen in acute and chronic pancreatitis.

According to the Marseilles-Rome classification of 1988, the term *acute pancreatitis* is used to refer to single or repeated episodes of abdominal pain associated with a range of potentially reversible pancreatic lesions including pancreatic edema, necrosis, and hemorrhage, as well as peripancreatic fluid collections, necrosis, and pseudocysts. *Chronic pancreatitis* is used to refer to recurrent or persistent abdominal pain that is associated with irreversible and ongoing inflammatory destruction of exocrine parenchyma and eventually, islets. In practice, however, the distinction between acute and chronic pancreatitis is rarely made based on tissue sampling, and there is no consensus on the definition of irreversible morphological change.\(^1\) It is also acknowledged that certain forms of chronic pancreatitis can occur in the absence of pain.

The Marseilles-Rome classification further divides chronic pancreatitis into several morphological subtypes that may coexist in the same patient. *Chronic obstructive pancreatitis* is characterized by exocrine atrophy and is associated with duct stenosis caused by tumors, pseudocyst, or scarring from prior acute pancreatitis. *Chronic calcifying pancreatitis* is characterized by intraductal calcifications and protein plugs, and is often associated with atrophy, stenotic ducts, and areas of acute inflammation or pseudocyst. *Chronic inflammatory pancreatitis* consists of dense infiltration of mononuclear inflammatory cells. *Retention cysts* and *pseudocysts*, seen in
both calcifying and obstructive forms, may also become infected. *Fibrosis* may develop in the absence of symptoms.

Chronic pancreatitis lacks a simple unifying theory of disease pathogenesis. The precise mechanism by which any specific agent or circumstance induces pancreatitis remains obscure. Acute pancreatitis clearly has the potential to evolve into chronic disease. However, repeated episodes of acute pancreatitis do not invariably lead to chronic pancreatitis, and chronic pancreatitis may present without prior acute attacks. Excessive alcohol ingestion has been associated with chronic pancreatitis since the term was introduced by Comfort in 1946. Alcohol use continues to be the most commonly identified environmental risk factor clinically. The precise relationship between alcohol and chronic pancreatitis remains, however, poorly understood. Alcohol ingestion does not lead to pancreatitis in experimental animal models. Alcoholism is by no means uniform among human pancreatitics. Chronic pancreatitis in humans occurs in the absence of significant alcohol usage, and fewer than 5% of alcoholics actually develop pancreatic disease. Acute and chronic forms of pancreatitis have been associated with exposure to toxic agents other than alcohol. As with alcohol, most individuals exposed to the other toxic substances associated with pancreatitis do not develop the chronic form of the disease.

Given the lack of an identified, uniform pathogenic trigger, the concept of risk modifiers rather than etiologies or causes of chronic pancreatitis may be more appropriate in classifying the disease, particularly when making decisions regarding patient management. Chronic pancreatitis is not simply a “drunkard’s disease,” but rather is more appropriately attributed to a variety of genetic, environmental, anatomic, immunologic, and other poorly understood susceptibility factors that interact to initiate and perpetuate the pathology. Whitcomb has proposed the TIGAR-O system (Table 71-1) as a potential framework that allows various risk factors associated with the disease to be logically organized into categories: Toxic or metabolic, Idiopathic, Genetic, Autoimmune, Recurrent acute, and Obstructive. The TIGAR-O system reflects the fact that in chronic pancreatitis there is a diversity of etiologic risk factors that contributes to a spectrum of pathological and functional derangements, clinical features, and natural history.
TABLE 71-1: TIGAR-O CATEGORIZATION OF RISK FACTORS FOR CHRONIC PANCREATITIS

Toxic/metabolic
   Alcohol
   Tobacco
   Hypercalcemia (hypoparathyroidism)
   Dietary/nutritional (tropical)
   Hyperlipidemia
   Chronic renal failure (uremia)

Idiopathic

Genetic
   PRSS1, PRSS2
   SPINK1
   CFTR
   Chymotrypsin C

Autoimmune

Recurrent and severe acute pancreatitis

Obstructive/mechanical
   Pancreas divisum
   Sphincter of Oddi dysfunction
   Annular pancreas
   Malignant obstruction of the pancreatic duct
   Primary pancreatic duct stones
   Choledochocole


Toxic or Metabolic

The majority of patients with chronic pancreatitis (55%-80%) will report significant alcohol intake over the years prior to diagnosis. A relationship between dose and duration of alcohol use has been repeatedly documented,
and there appears to be a threshold level for the risk of pancreatitis at approximately 50 g (four drinks) per day. Several mechanisms have been proposed to account for pancreatic injury, including alterations in pancreaticobiliary secretory flow, ductal plugging, and direct toxic action on acinar cells. Chronic pancreatitis in the setting of alcohol use is associated with pancreatic calcification and ductal stone formation, but none of the proposed mechanisms is convincingly supported experimentally, and the hypotheses are not mutually exclusive. Several other toxic agents have been identified as risk factors for pancreatitis. Included among these is tobacco, which has been shown to confer increased risk of chronic pancreatitis independent of alcohol use. Several medications have been implicated in acute pancreatitis but probably do not play a role in the chronic form of the disease. Similarly, hypercalcemia (eg, associated with hyperparathyroidism) and various forms of hyperlipidemia (eg, hypertriglyceridemia) are linked to acute but not chronic pancreatitis. So-called tropical chronic pancreatitis, described in children living in developing parts of the world, is thought to be either due to a dietary toxin or to an unidentified micronutrient deficiency.

**Idiopathic**

About 20% of patients with chronic pancreatitis have no clinically obvious risk factor. It is suspected that a great many of these idiopathic cases will ultimately prove to harbor yet-unidentified genetic or molecular derangements that explain the process. In recent years, many patients previously considered to be idiopathic recurrent acute and chronic pancreatitis have been found to carry mutations, polymorphisms, or splice variants of the gene associated with cystic fibrosis (CF). Recent evidence also suggests that polymorphisms in genes associated with oxidative stress and xenobiotic metabolism may be more prevalent in patients with what is now characterized as idiopathic disease. Thus, as new genetic associations that predispose to the development of chronic pancreatitis become recognized, the percentage of patients with truly idiopathic disease will decrease.

**Genetic**

Hereditary pancreatitis was first characterized in 1952 as early onset of
chronic pancreatitis clustering in family members without other risk factors.\textsuperscript{8} At least half of hereditary pancreatitis kindreds have been found to carry germline mutations in the cationic trypsinogen (PRSS1) gene.\textsuperscript{3,4,9} The arginine-to-histidine (R122H) substitution is the most common defect. Hereditary pancreatitis has an autosomal dominant pattern of inheritance, with a high degree of penetrance. Cationic trypsinogen is produced in the pancreatic acinar cells and, upon cleavage by duodenal enteropeptidase, forms trypsin. Trypsin is a protease that acts to hydrolyze dietary proteins and plays the key role in both initial activation of other pancreatic zymogens (including trypsinogen itself) and in their subsequent proteolytic inactivation. Trypsin encoded by pancreatitis-associated PRSS1 mutations is unusually stable and resists autolytic inactivation, predisposing to premature and extended activation of trypsin within the pancreatic parenchyma.\textsuperscript{10} Mutations in other genes such as anionic trypsinogen (PRSS2) or the calcium-sensing receptor (CASR) have also been reported in some cases of hereditary pancreatitis, although in many other kindreds, the responsible gene has not yet been identified.\textsuperscript{11} Other gene associations with hereditary or otherwise idiopathic chronic pancreatitis will undoubtedly emerge over the next several years. Recently, for example, inactivating mutations in the gene encoding for the trypsin-degrading enzyme chymotrypsin C have been identified in a German cohort.\textsuperscript{12}

Another genetic disorder associated with pancreatic pathology is CF, a disease linked to mutations in the CF transmembrane conductance regulator (CFTR) gene.\textsuperscript{9,13–15} CFTR is a chloride ion channel involved in water, chloride, and bicarbonate secretion by epithelial cells such as those lining the gastrointestinal tract and respiratory system. In the pancreas, CFTR is localized to centroacinar and proximal lobular duct cells.\textsuperscript{16} Over 90% of CF patients are pancreatic insufficient, and while severe pancreatic fibrosis is common, acute pancreatitis is rare.\textsuperscript{17} However, a subset of patients with otherwise idiopathic recurrent acute and chronic pancreatitis has been noted to have borderline abnormalities in functional tests for CF such as sweat chloride content. These patients harbor at least an eightfold increase in CF-associated CFTR mutations on a single allele. Various other CFTR mutations, polymorphisms, and splice variants not associated with classical pulmonary manifestations of CF are also frequently identified in patients with recurrent acute and chronic pancreatitis. The CFTR gene shows autosomal
recessive inheritance with incomplete penetrance, and thus a family history of CF or pancreatic disease is usually absent in CFTR-associated pancreatitis. The mechanism of CFTR-associated pancreatitis is thought to involve the viscous, low-volume, low-bicarbonate containing pancreatic fluid secretion leading to duct sludge, ductal obstruction, and enzyme hyperconcentration, enhancing the potential for intraglandular enzyme activation.

Mutations and polymorphisms in other genes may also modify susceptibility to chronic pancreatitis. Pancreatic serine protease inhibitor Kazal type 1 (SPINK1) is a natural protease inhibitor that localizes with trypsinogen within zymogen granules. SPINK1 binds to and inhibits activated trypsin, thus serving as a “buffer” of sorts against inappropriate early trypsinogen activation. Mutations of the SPINK1 gene (notably N34S) appear to increase the risk of recurrent acute and chronic pancreatitis, particularly in patients who harbor two mutated alleles. A single mutated SPINK1 allele appears to increase the risk of alcohol-associated pancreatitis and tropical pancreatitis.

**Autoimmune**

Autoimmune pancreatitis (AIP), also known as lymphoplasmocytic sclerosing pancreatitis, is characterized by diffuse glandular enlargement and infiltration with CD4- or CD8-positive lymphocytes and IgG4-positive plasma cells. The exact immunologic etiology is unknown, although circulating antibodies with homology both to a peptide sequence associated with a protein from *Helicobacter pylori* (infection with which is associated with various autoimmune disorders including AIP) and to a protein highly expressed in pancreatic acinar cells have recently been found in over 90% of patients. Inflammatory infiltrates are particularly concentrated in duct rather than acinar zones, however, and thus a duct-origin autoantigen has been postulated. Notably, diffused ductal narrowing rather than dilation is usually observed. Initially described predominately in young men, AIP has been increasingly recognized as a cause of biliary obstruction and pseudotumor in older individuals. Most patients report little in the way of pain, and prior attacks of acute pancreatitis are unusual. It has been associated with serologic elevation of IgG4 levels in about two-thirds of patients and with other autoimmune conditions in approximately 20%, including Crohn’s disease,
ulcerative colitis, Sjögren syndrome, primary biliary cirrhosis, or primary sclerosing cholangitis.18,21

Recurrent and Severe Acute Pancreatitis

Recurrent episodes, or even a single severe episode of acute pancreatitis, may lead to chronic pancreatitis, but the basis for progression is poorly understood. Patients with prior episodes of necrosis appear to be at particular risk for developing chronic disease. In many cases, progression may be due to postpancreatic ductal scarring, persistent activation of pancreatic stellate cells, and neuroplasticity leading to hyperalgesia.

Obstructive

Post-traumatic duct strictures, or obstruction associated with tumors including cystic neoplasms, neuroendocrine lesions, and pancreatic adenocarcinoma have been associated with pancreatic pathology consistent with chronic pancreatitis, although these patients are often asymptomatic. Chronic pancreatitis has also been associated with anomalous anatomic variations in the pancreatic ductal system, most notably pancreas divisum, and it has been postulated that relative obstruction to pancreatic flow through the dorsal duct and minor papilla predisposes to recurrent acute and chronic pancreatitis. The evidence supporting the association to chronic pancreatitis in particular is largely circumstantial and may reflect referral bias,22 but pancreas divisum may be a contributing factor in the presence of certain genetic risk factors (Fig. 71-1). Some cases of chronic pancreatitis are attributed to sphincter of Oddi dysfunction, although rigorous evidence to support this association is also lacking.
FIGURE 71-1 Recurrent acute and chronic pancreatitis in a 41-year-old woman with pancreas divisum and a pancreatitis-associated mutation in the cystic fibrosis (CF) gene. Magnetic resonance cholangiopancreatography (MRCP) demonstrates noncommunicating dorsal (arrow) and ventral (arrowhead) pancreatic ducts.

PATHOPHYSIOLOGY AND MECHANISM OF PAIN

Progress in elucidation of the pathogenesis of chronic pancreatitis has been hampered by the lack of a suitable experimental model that adequately recapitulates the features of the disease seen in humans. However, existing evidence suggests a number of useful conceptual frameworks that may help guide efforts to treat patients with chronic pancreatitis. Traditional theories of
the pathogenesis of acute pancreatitis include the toxic-metabolic or oxidative stress hypotheses, in which normal acinar cell processing and release of zymogens are disrupted by a toxic or oxidative stressor, and the ductal obstruction hypothesis that proposes a mechanical role for ductal plugs and stones causing disruption of the integrity of the acinar cell (common in alcoholic and tropical disease). In certain situations, notably autoimmune disease, pancreatitis may begin not in the acinar cell but in the duct cell, triggered by the development of an as-yet-unidentified autoantigen on the duct epithelium. Recently, attention has focused on understanding the mechanism of pancreatic fibrosis, the central histological feature that characterizes the evolution from acute disease to chronic pancreatitis. One attractive hypothesis is that a sentinel acute pancreatitis event (SAPE) primes the pancreas for fibrogenesis. According to the SAPE concept, local inflammatory cytokines released during acute pancreatitis activate circulating macrophages that infiltrate the gland as well as resident pancreatic stellate cells, myofibroblast-like cells that are normally quiescent. During the subsequent healing phase, anti-inflammatory mediators (particularly anti-inflammatory cytokines such as tumor growth factor beta [TGF-β]) drive stellate cells and tissue macrophages to synthesize and deposit fibrogenic matrix proteins. The pancreatic parenchyma may return to normal after a mild self-limited episode. However, the damage may not completely resolve after a severe attack, particularly if there has been significant tissue necrosis. Thus, following the SAPE, the local pancreatic environment may be permanently altered by the persistent presence of anti-inflammatory and profibrogenic cell populations that are perpetually activated by ongoing toxic-metabolic, oxidative, or mechanical stress. The pancreas then becomes subject to repeated cycles of inflammation and progressive fibrosis.

A comprehensive mechanistic explanation for pain, often the most debilitating symptom of chronic pancreatitis, also remains elusive. One hypothesis is that pain results from capsular stretch associated with ductal or organ hypertension. This hypothesis is supported by the favorable results of surgical or endoscopic ductal drainage in patients with chronic pancreatitis associated with dilated pancreatic ducts, and the success of surgical resection in other selected patient populations. An alternative, possibly complementary, hypothesis is that the pain represents a neuropathy caused by repeated inflammatory insults and damage to retroperitoneal sensory nerves. Recent evidence demonstrating neuroplasticity in nociceptive dorsal root
ganglia in chronic inflammatory states, with evidence of upregulation of nociceptors such as TRPV1 by proteolytic enzymes such as trypsin, supports this theory.

**CLINICAL PRESENTATION**

As in acute pancreatitis, pain in chronic pancreatitis typically localizes to the left upper quadrant or epigastric region, often radiating around or into the back. The pattern of pain is variable. Some patients experience recurrent attacks of moderate to severe pain interspersed with periods of relative or complete quiescence. In others, the pain may be persistent and lead to significant incapacitation and chronic disability. During acute exacerbations, the pain may be increased by food intake and is frequently associated with nausea and vomiting.

Weight loss and malnutrition are common, due to both decreased intake as well as exocrine insufficiency, with consequent malabsorption of protein and fat. Exocrine insufficiency is usually obvious in patients with classical steatorrhea (loose, bulky bowel movements that may be greasy, sticky, oily, or foul-smelling), but these symptoms are obscured by narcotic-associated constipation.

Endocrine insufficiency typically occurs late in the course of disease, often after exocrine insufficiency has appeared, and usually not before about 90% of the pancreatic parenchyma has been replaced by fibrosis. For reasons that are unclear, there is a relative sparing of islet cells until late in the course of the disease. Diabetes is more common in patients with alcohol-associated chronic calcifying pancreatitis, with 80% of these individuals demonstrating endocrine insufficiency within 10 years of the development of severe exocrine insufficiency. Histologically, pancreatic islets are seen to persist within areas of extensive fibrotic replacement of exocrine tissue (Fig. 71-2). Because diabetes of chronic pancreatitis is associated with indiscriminate destruction of all cell types within the islets of Langerhans, counterregulatory glucose control may be considerably more labile than in either type I or type II diabetes. Less is known regarding the natural history of nonalcohol-associated chronic pancreatitis, but the risk of diabetes appears to be lower. Both endocrine and exocrine insufficiency occur later and less frequently in patients with chronic pancreatitis associated with gene mutations than those
without gene mutations.\textsuperscript{28}

![Histopathology of chronic pancreatitis showing islet entrapment within exocrine parenchymal fibrosis. (Used with permission from Dr. Jerrold Turner.)(715846) (715850)](https://example.com)

**FIGURE 71-2** Histopathology of chronic pancreatitis showing islet entrapment within exocrine parenchymal fibrosis. (Used with permission from Dr. Jerrold Turner.)

On occasion, the initial manifestation of chronic pancreatitis will be related to extrapancreatic complications such as intestinal or biliary obstruction due to compression by a pseudocyst or progressive peripancreatic fibrosis and gastrointestinal hemorrhage due to blood lost into the pancreatic duct (*hemosuccus pancreaticus*) or due to rupture of pseudoaneurysm into a pseudocyst or to splenomesenteric vein thrombosis.

**DIAGNOSIS**

The diagnosis is usually suspected based on an appropriate clinical history and is confirmed by imaging studies. Laboratory investigation is of limited value. Acute exacerbation of abdominal pain may be paralleled by a transient increase in serum amylase or lipase, but these may be normal with progressive destruction of acinar cell mass. Elevation of liver function tests, particularly serum bilirubin and alkaline phosphatase, may indicate the presence of bile duct obstruction.

The diagnosis of chronic pancreatitis is usually confirmed by imaging studies, most commonly computed tomography (CT). CT findings depend on
the morphologic type of chronic pancreatitis, the duration of disease, and the presence of complications. In the early phases of chronic pancreatitis, ductal or parenchymal changes may be rather subtle, but as the disease advances, progressive and irreversible changes in organ architecture are readily apparent. Chronic pancreatitis associated with toxic-metabolic or genetic risk factors, and idiopathic chronic pancreatitis may demonstrate calcifications either focally or scattered throughout the organ. There may be evidence of acute inflammatory changes or focal areas of enlargement associated with areas of dense calcifications, particularly in the pancreatic head (Fig. 71-3); this so-called “inflammatory head mass” appears to be more common in European than American cohorts. There may be evidence of segmental or diffuse pancreatic ductal dilation related to stricture formation, and pseudocyst formation and evidence of extrapancreatic complications such as duodenal or biliary obstruction, or splenomesenteric vein thrombosis (Fig. 71-4). In AIP, calcifications are almost uniformly absent and the pancreas is usually diffusely enlarged, although a focal mass-forming variant is occasionally encountered. In obstructive forms of chronic pancreatitis, the pancreatic duct is dilated upstream of the area of stenosis, and the acinar parenchyma appears atrophic.
FIGURE 71-3 Axial cross-sectional abdominal CT demonstrating enlargement and dense calcifications (*arrow*) in the pancreatic head in alcohol-associated chronic pancreatitis.
Pancreatic ductography complements CT imaging. Endoscopic retrograde cholangiopancreatography (ERCP) has long served as a gold standard of sorts in mapping duct pathology and offers endotherapeutic options including sphincterotomy and stent placement (Fig. 71-5). Magnetic resonance cholangiopancreatography (MRCP) is less invasive and provides image quality that rivals ERCP; the addition of secretin stimulation further enhances duct visualization and allows some assessment of pancreatic exocrine function (Fig. 71-6). Anatomic ductal anomalies such as pancreas divisum are readily defined by ERCP or MRCP, as are dominant focal duct strictures that might be amenable to endoscopic stenting or surgical drainage procedures. MR imaging integrates information regarding parenchymal and ductal involvement and may be particularly helpful when the disease is regionally heterogeneous and architecturally complex.
FIGURE 71-5 ERCP image showing classic diagnostic features of chronic pancreatitis including marked main duct dilation, intraluminal filling defects (stones), clubbing of side-branches, and areas of duct stricture.
FIGURE 71-6 Secretin-stimulated MRCP shows a diffusely dilated main pancreatic duct with obstruction to pancreatic flow associated with a dorsal duct stricture in the setting of pancreas divisum and chronic pancreatitis.

It is not difficult to establish the diagnosis of chronic pancreatitis in its advanced stages, when classical clinical symptoms are present or when imaging studies demonstrate obvious abnormalities such as strictures, ductal dilation, or pancreatic calcifications. Recognition of disease in its earlier stages presents more of a challenge. A 1983 conference held in Cambridge, England categorized chronic pancreatitis as equivocal, mild, moderate, or marked, and established criteria (Table 71-2) according to combinations of features seen in the main and side branch pancreatic ducts on CT and ductograms.\textsuperscript{1,31,32} Although this consensus approach has proven useful over the years, there continues to be a subset of patients with symptoms suspicious for chronic pancreatitis but in whom imaging studies are negative. Some of
these patients may suffer from functional abdominal pain disorders rather than pancreatic disease. Others may have early forms of chronic pancreatitis. Consensus workshops by the Japan Pancreas Society (1995 and 2001) continue to address the ongoing challenge of so-called “minimal change” disease in the context of evolving imaging and diagnostic modalities.

**TABLE 71-2: CAMBRIDGE CLASSIFICATION OF CHRONIC PANCREATITIS BASED ON ENDOSCOPIC RETROGRADE PANCREATEOGRAPHY**

<table>
<thead>
<tr>
<th>Grade of Pancreatitis</th>
<th>Main Pancreatic Duct Appearance</th>
<th>Side Branch Pancreatic Duct Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Equivocal</td>
<td>Normal</td>
<td>&lt;3 abnormal branches</td>
</tr>
<tr>
<td>Mild</td>
<td>Normal</td>
<td>&gt;3 abnormal branches</td>
</tr>
<tr>
<td>Moderate</td>
<td>Abnormal</td>
<td>&gt;3 abnormal branches</td>
</tr>
<tr>
<td>Marked</td>
<td>Abnormal plus any of the following:</td>
<td>&gt;3 abnormal branches</td>
</tr>
<tr>
<td></td>
<td>Cavity &gt;10 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stricture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intraductal filling defects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic calcification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contiguous organ involvement on CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe duct dilation or irregularity</td>
<td></td>
</tr>
</tbody>
</table>


Endoscopic ultrasound (EUS) appears to be valuable in evaluation of the suspicious pancreatic mass and in characterizing cystic lesions of the pancreas. EUS generally adds little to the evaluation of chronic pancreatitis in its advanced stages but has potential applicability in early-stage minimal-change disease where other imaging modalities fail to establish the diagnosis. EUS appears to be more sensitive than ERCP or MRCP in detecting early parenchymal fibrosis and subtle ductal changes occurring in
early forms of chronic pancreatitis. Various systems using up to 11 different parenchymal and ductal endosonographic criteria (Table 71-3) to diagnose chronic pancreatitis have been proposed. There is, however, no gold standard grading system or agreement on the threshold number of abnormalities that must be present for the diagnosis of chronic pancreatitis. Because of this, the value of EUS in making an early diagnosis of chronic pancreatitis remains uncertain. EUS may have more practical utility in cases of suspected AIP. Surgical interventions may be avoided in some of these patients who present with a mass-forming variant by EUS-directed core needle biopsy demonstrating the pathognomonic lymphoplasmacytic infiltrate and thus ruling out malignancy.

<table>
<thead>
<tr>
<th>Parenchymal Criteria</th>
<th>Ductal Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperechoic foci</td>
<td>Main pancreatic duct dilation</td>
</tr>
<tr>
<td>Hyperechoic strands</td>
<td>Duct irregularity</td>
</tr>
<tr>
<td>Lobularity of the gland</td>
<td>Hyperechoic duct margins</td>
</tr>
<tr>
<td>Cysts</td>
<td>Dilated side branches</td>
</tr>
<tr>
<td></td>
<td>Stones</td>
</tr>
</tbody>
</table>


Functional testing to demonstrate pancreatic exocrine insufficiency is occasionally helpful, although from a practical standpoint, the condition is usually clinically obvious. Symptoms of steatorrhea, postprandial gaseous distension, or progressive weight loss despite adequate caloric intake are all suggestive of exocrine insufficiency. Quantification of fecal fat content or measurement of fecal human elastase (FE-1) levels can confirm the diagnosis and can be used to monitor efficacy of enzyme supplementation and surgical intervention. Unfortunately, these studies are most reliable in those patients in whom the diagnosis is clinically obvious. They are of questionable accuracy in the setting of patients with more subtle symptoms where objective documentation of exocrine insufficiency might be most needed.
Elevation in fasting serum glucose or glycosylated hemoglobin (HgA1c) suggests pancreatic diabetes. Functional evaluation (eg, formal oral glucose or arginine-tolerance testing) for pancreatic endocrine insufficiency may be helpful in patients prior to pancreatic resection, particularly if autologous islet transplantation is under consideration.

In patients with suspected AIP, measurement of serum immunoglobulin G levels, particularly IgG4, is indicated. Other markers of autoimmune disease include rheumatoid factor, antinuclear antibody, C-reactive protein (CRP), or erythrocyte sedimentation rate, although these are less specific.  

The role of genetic testing in patients with idiopathic or suspected hereditary pancreatitis is controversial. It may be most reasonable to screen for PRSS1 mutations in patients with a strong family history of pancreatitis because of the autosomal dominant inheritance and the high risk of development of pancreatic cancer—a risk that is further dramatically elevated by tobacco use. However, hereditary pancreatitis patients without PRSS1 mutations may have the same elevated risk of cancer, and there is no evidence that screening by serial imaging studies leads to earlier diagnosis or improved prognosis of pancreatic cancer. Identification of CFTR or SPINK1 gene mutations may be useful in selected circumstances; for example, patients with idiopathic pancreatitis may feel reassured by having an “explanation” for their disease. In the absence of therapy directed at the specific functional defects associated with these mutations, however, the clinical value of gene testing is debatable. Genetic counseling is highly advisable in the context of whether to perform genetic testing and in interpretation of the results.

**MEDICAL MANAGEMENT**

Cessation of potential inciting agents such as alcohol may reduce the intensity or frequency of exacerbations of chronic pancreatitis. Avoidance of high-fat foods and tobacco use may also be of value. Occasionally, patients are unable to tolerate oral food intake for extended periods of time, in which case nutritional support by an enteral route that minimizes pancreatic stimulation (eg, via nasojejunal or gastrojejunal tube) or by a parenteral approach may be required. Pancreatic enzyme replacement is used to treat steatorrhea and other symptoms of exocrine insufficiency. Enteric-coated
preparations are most useful in this setting. Various formulations differ in lipase, protease, and amylase content, and enzyme replacement therapy should be titrated to effect. Patients must be carefully instructed to time enzyme ingestion appropriately in relation to meals to optimize mixing.

In certain circumstances, medical therapy may alter the intensity or frequency of attacks. For example, some patients with early, small duct, or minimal change disease appear to benefit from high doses of noncoated enzyme preparations. The presence of activated enzymes within the duodenum has been shown to decrease cholecystokinin-mediated stimulation of the pancreas. Noncoated enzyme preparations must be protected from destruction by gastric acid suppression therapy; trials that instead utilize enteric-coated delayed-release enzyme formulations showed no benefit. Several randomized trials suggest that a five-component antioxidant regimen reduces the frequency and intensity of painful episodes. Patients with AIP confirmed by elevated IgG4 levels or tissue biopsy may be treated with an 8-week tapering course of corticosteroids to positive effect, including resolution of jaundice related to mechanical biliary obstruction.

The major reason patients with chronic pancreatitis seek medical attention is unrelenting or frequently relapsing pain. Pain, more than any other feature, accounts for intractability and overall loss of quality of life. While in some patients, the intensity of pain may burn out as the disease reaches its end stage, the natural history is highly variable and it may take years for relapsing episodes of pain to relent, if it occurs at all. Thus, a conservative, watch-and-wait approach is rarely acceptable. Pharmacotherapy for pain should begin with nonsteroidal anti-inflammatory medications, but if more powerful agents are needed, propoxyphene or tramadol may be used prior to escalating to more aggressive pharmacotherapy. Long-acting narcotics supplemented by short-acting narcotic formulations for breakthrough pain may be more effective than short-acting agents alone. Unfortunately, narcotic dependency is a common consequence of the use of these agents. Psychosocial supports such as counseling are essential to successful longitudinal management of chronic pain. Variable results have been reported with the use of long-acting somatostatin analogues. Occasionally, tricyclic antidepressants or gabapentin may be useful. Alternatives such as placement of infusion pumps for intrathecal delivery of narcotics have been anecdotally successful.
Neurolysis may be considered in patients who have failed medical management and who do not appear to have favorable anatomic circumstances amenable to endoscopic or surgical intervention. The most common neurolytic procedure is celiac plexus block, which can be performed under radiological or endoscopic guidance. The initial approach involves injection of a combination of steroids and a local anesthetic into the celiac ganglion. If temporary relief is obtained, this is followed by permanent neurolysis with 100% alcohol injection. Results of celiac plexus block in chronic pancreatitis have been mixed, but transient improvement (typically no more than 6 months) may be of benefit in selected patients.\textsuperscript{36,46} Splanchnicectomy, usually performed by a thoracoscopic approach, has also been used, but similar to other forms of neurolysis, permanent resolution of pain is unusual.\textsuperscript{47}

Therapeutic endoscopic intervention may be considered in patients with obstructive and inflammatory disease. Lithotripsy of pancreatic duct stones and pancreatic duct stent placement has been reported in several small retrospective series. Technical success can be reliably achieved in appropriately selected patients (eg, manageable stone size and local density sufficiently close to the working end of the scope and without intervening duct stricture). However, the effectiveness of endotherapy over time is often less than 50% with respect to improvement in pain or reduction in frequency of attacks. Multiple procedures are often necessary, recurrence of strictures and stones is frequent, and the substantial fraction of patients who fail generally require surgical intervention (Fig. 71-7).\textsuperscript{48,49} Long-term presence of stents within the pancreatic duct may worsen inflammatory ductal strictures, although most series find a few patients who achieve durable pain relief following removal of stents. Patients who are suitable for endotherapy are usually also candidates for surgical intervention, provided there are no medical contraindications to operation. The two randomized trials (Table 71-4) to date that directly compared surgical therapy to endoscopic stenting reported long-lasting superiority of the surgical approach with respect to pain relief, quality of life over time, and other endpoints.\textsuperscript{50,51}
FIGURE 71-7 Coronal CT image of a biliary endoprosthesis in a patient with chronic calcifying pancreatitis. Attempts at endoscopic pancreatic duct stone removal were unsuccessful, and the patient underwent pancreaticoduodenectomy.

TABLE 71-4: RANDOMIZED COMPARISONS OF ENDOSCOPIC STENTING TO SURGICAL MANAGEMENT FOR MAIN DUCT DILATION

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Surgical Procedures</th>
<th>Number of Patients</th>
<th>% With Durable Pain Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Endo Stenting</td>
<td>Surgery</td>
</tr>
<tr>
<td>Dine56</td>
<td>2003</td>
<td>Resection and drainage</td>
<td>36</td>
<td>36</td>
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SURGICAL MANAGEMENT OF CHRONIC
PANCREATITIS

Surgical therapy for chronic pancreatitis is usually reserved for patients with symptoms that are otherwise intractable to pharmacotherapy and other therapeutic approaches. In over 90% of patients, the main indication for operation is pain. Occasionally, an operation is performed to relieve biliary or gastrointestinal obstruction, to internally drain a symptomatic pseudocyst, or for vascular complications of chronic pancreatitis such as gastric variceal hemorrhage secondary to splenic vein thrombosis.

Operations on the pancreas when done in the context of chronic pancreatitis are typically technically demanding and carry significant risks of postoperative morbidity and mortality. Although in appropriately selected patients, the immediate results may be excellent, long-term success (durable pain relief) is achieved in at most 85% of patients at 5 years of follow-up. The optimal timing of a surgical intervention continues to be a subject of considerable debate. Most practitioners make an effort to hold off on intervention until all medical and endoscopic options have been exhausted, while others have begun to advocate for a more expeditious move to surgery in these patients under the notion that early definitive intervention may obviate risk of a permanent, refractory retroperitoneal neuropathy. There is little objective data available to guide decisions on timing of intervention in patients who have pain as their predominant symptom. One recent study presented from the Dutch Pancreatitis Study Group retrospectively evaluated 266 patients treated with surgical intervention for chronic pancreatitis and noted that surgery done within 3 years of symptoms was independently associated with more significant postoperative pain relief and less endocrine insufficiency.\textsuperscript{52}

A number of pancreatic operations have been developed over several decades of international effort. These operations generally involve either ductal drainage, parenchymal resection, or some combination of resection and ductal drainage. The choice of operation depends on the anatomic morphology of the disease process. In many patients, the disease appears to be driven predominantly by pathology within the pancreatic head, sometimes considered the “pacemaker” of chronic pancreatitis, particularly in those with a sizable inflammatory mass in this region of the organ. Others present more diffuse disease involving extensive areas of stricture and dilation of the main pancreatic duct or its ductal tributaries. Occasionally, disease appears limited
to the body or tail. Alternatives for surgical intervention are best individualized and considered in the context of the most frequently encountered clinical and anatomic scenarios.

**Large-Duct Disease**

Large-duct chronic pancreatitis is characterized by enlargement of the main pancreatic duct lumen to a diameter exceeding 7 to 8 mm. Ductal dilation is often diffuse along the length of the organ, but there may be one or more intervening areas of ductal stricture. In many patients, calcific deposits (stones) may be evident on imaging studies within the main or secondary ducts.

Puestow described a procedure to provide enteric drainage to a diffusely dilated main pancreatic duct, with the goal of achieving pain relief by duct decompression. In its initial description, the Puestow procedure consisted of a longitudinal unroofing of the dilated pancreatic duct in the body and neck of the gland, and also involved resection of the pancreatic tail. A long-segment longitudinal pancreaticojejunostomy was then constructed to establish enteric drainage. A modification reported by Partington and Rochelle in 1960 eliminated the distal pancreatectomy. Lateral pancreaticojejunostomy is thus now referred to as either a (modified) Puestow or Partington-Rochelle procedure and continues to be commonly used for disease characterized by a diffusely dilated main pancreatic duct with no mass and no significant biliary obstruction in the pancreatic head.

**LATERAL PANCREATICOJEJUNOSTOMY—TECHNIQUE**

Midline or transverse upper abdominal incisions provide acceptable exposure for this procedure. The dissection is begun by incising the peritoneal lining adjacent to the lateral border of the second portion of the duodenum, extending laterally to release the hepatic flexure of the right colon. Using electrocautery, the retroperitoneal attachments lateral and posterior to the duodenum are divided to widely mobilize the duodenum and posterior aspect of the head of the pancreas (Kocher’s maneuver). This dissection is carried inferiorly to free the third portion of the duodenum from the base of the transverse mesocolon, effectively exposing the head of the pancreas and
anterior surface of the duodenum from the pylorus to the level of the superior mesenteric vessels. Exposure of the anterior surface of the pancreatic body and tail requires access to the lesser sac, which is entered by dividing the gastrocolic omentum or by separating the avascular plane of attachment from the transverse colon and mesocolon. Next, the gastroduodenal artery (GDA) is identified at its supraduodenal origin from the common hepatic artery and traced across the head of the pancreas. The GDA is then suture ligated at both the superior and inferior border of the head of the pancreas in an effort to prevent intraoperative hemorrhage during incision of the pancreatic head and main pancreatic duct during the dissection as well as postoperative bleeding at the site of the pancreaticojejunostomy. The anterior surface of the pancreas is then carefully examined to confirm the presence of main duct dilation and the absence of suspicious mass lesions or unanticipated inflammatory changes in the head of the gland. The dilated pancreatic duct is usually visible by direct inspection or palpation of the anterior surface of the pancreas but can also be accessed by means of a fine needle and low-volume syringe. The duct can also be localized using intraoperative ultrasound, but this is usually not necessary. The pancreatic duct is then incised longitudinally along its full length using electrocautery. This ductotomy should extend across the neck into the head of the organ where the GDA traverses the pancreas, and should extend laterally as far as possible along the length of the tail so that the entire segment of dilated duct is unroofed. The pancreaticojejunal anastomosis is performed in Roux-en-Y fashion using a 40- to 50-cm defunctionalized jejunal limb. Using a linear gastrointestinal stapler, the proximal jejunum is divided at the apex of a mesojejunal vascular arcade of suitable mobility, typically at least 20 to 30 cm distal to the ligament of Treitz, although the precise distance is probably unimportant. The distal staple line is inverted using a series of 3-0 silk sutures placed in a Lembert fashion, which are tied (but not cut) and then held by a fine clamp that facilitates later positioning of the pancreatic anastomosis. Intestinal continuity is then reestablished by a handsewn or stapled enteroenterostomy such that the intestinal conduit is approximately 60 cm in length. The Roux limb is then advanced through the transverse mesocolon either to the right or left of the middle colic vessels. A longitudinal jejunostomy is made to correspond to the pancreatic ductotomy. The pancreaticojejunal anastomosis is handsewn with a running absorbable suture (eg, 4-0 double-armed polyglyconate or polydioxanone suture), which, according to surgeon
preference, may be additionally reinforced by an outer later of interrupted nonabsorbable suture (Fig. 71-8). After completion of the anastomosis, the distance between the pancreaticojejunostomy and the enteroenterostomy should measure at least 40 cm to prevent reflux of enteric contents up to the anastomosis.

**FIGURE 71-8** Cross-section of the anastomosis for a lateral pancreaticojejunostomy (applies to Puestow, Frey, or Izbicki procedures).

**LATERAL PANCREATICOJEJUNOSTOMY—OUTCOMES**

Results of the Partington-Rochelle procedure in appropriately selected patients are generally favorable. In most series, 75% to 80% of patients with diffusely dilated main pancreatic ducts (>7 mm) and no dominant inflammatory mass have achieved durable pain relief over 5 to 10 years of follow-up.\(^{53,55–58}\) Compared to other major pancreatic operations, perioperative morbidity is low, and because no pancreatic parenchyma is removed, endocrine and exocrine functions are generally preserved relative to
preoperative levels. Failure of lateral pancreaticojejunostomy is usually due to inappropriate patient selection (underappreciated extent of disease with the presence of significant fibrosis in the pancreatic head), or ongoing fibrosis with the progressive development of neuropathic pain.

**Chronic Pancreatitis with a Dominant Pancreatic Head Mass**

Lateral pancreaticojejunostomy has limited applicability in patients without diffuse main duct dilation. Multiple groups have reported that an isolated drainage procedure in patients with complex inflammatory changes in the pancreatic head, body, or tail results in poor clinical outcome with quick recurrence of symptoms of pain and progression to exocrine insufficiency. For patients with an inflammatory mass, extensive calcifications, or duct stones in the pancreatic head, results appear to be better either with pure resectional or with hybrid resection and drainage procedures. The four procedures used with great frequency today are pancreaticoduodenectomy (Whipple procedure, with or without pyloric preservation) and three forms of duodenum-preserving pancreatic head resection (DPPHR): the Beger procedure, the Berne procedure, and the Frey procedure.

The outcomes associated with these procedures have been compared in several randomized trials enrolling small numbers of patients with head-predominant morphology. None of these studies has demonstrated any one of the techniques to be clearly superior to others (Table 71-5). There are no measurable differences in outcomes compared, the numbers in the trials are small, and the metrics used to evaluate the outcomes are variable and imperfect.59–62 As a result, no consensus opinion among pancreatic experts about which procedure is the best in any given clinical situation has emerged. In recent years, European surgeons have tended to favor a duodenum-preserving approach and American surgeons have tended to favor pancreaticoduodenectomy. One recent survey of American surgeons who were members of the Pancreas Club found that of 59 surgeons surveyed, only 34 had ever performed DPPHR and that only 23 US surgeons continue to perform these procedures on a regular basis.63
In spite of the lack of data supporting the relative superiority of any given procedure, we do believe that each has specific applicability to certain subtypes of head-predominant morphology. A reasonable approach is to tailor the procedure to the anatomic morphology seen on the preoperative axial imaging and ductography. Patients with a dominant head mass and a dilated main pancreatic duct but no biliary dilation may be best served by a Frey procedure (limited duodenum-preserving resection of the pancreatic head with extended lateral pancreaticojejunostomy). Patients with a dominant head mass without main duct dilation and no biliary obstruction may be better suited for the Berne modification of the Beger procedure (limited duodenum-preserving resection of the pancreatic head without extension of the lateral pancreaticojejunostomy toward the tail). Patients with biliary obstruction or imaging characteristics more suspicious for the presence of malignancy should probably undergo pancreaticoduodenectomy rather than any form of DPPHR.

**PANCREATICODUODENECTOMY—TECHNIQUE**

The early primary objective in the pancreaticoduodenectomy is making an efficient determination of whether or not the pathology allows safe resection. This typically involves a thorough manual examination of the abdomen to rule out metastatic cancer and then a rapid exposure of the pancreatic neck superiorly and inferiorly in an effort to assess the operator’s ability to free the
hepatic artery, superior mesenteric vein, and superior mesenteric artery from the pathology in the pancreatic head safely. Pancreaticoduodenectomy may be performed through a midline laparotomy or bilateral subcostal incision. Careful inspection and palpation of the peritoneal surfaces and liver is performed first, with frozen-section biopsy obtained of any suspicious lesions. Small areas of fat necrosis or fibrosis from prior attacks of pancreatitis are easily mistaken for metastatic deposits. The base of the transverse mesocolon should be inspected for evidence of foreshortening or inflammatory involvement that may herald a difficult or dangerous dissection in the vicinity of the superior mesenteric vessels, and to confirm the absence of otherwise unsuspected tumor extension. The hepatic flexure of the colon is mobilized by freeing the lateral retroperitoneal attachments using the electrocautery, an extended Kocher maneuver is performed, and the lesser sac is then entered by separation or division of the gastrocolic omentum, as described in the previous section. The mass in the head of the gland is palpated and determined to be safely free from the superior mesenteric vein (SMV) at the inferior border of the neck of the pancreas by preliminary dissection of the plane anterior to the SMV posterior to the neck of the pancreas. Attention is then turned to the supraduodenal region. A cholecystectomy is performed, and the portal dissection is initiated by isolating the common bile duct (CBD) at the level of the cystic duct stump. The bile duct is carefully freed from the anterolateral surface of the portal vein and secured temporarily with a vessel loop. The common hepatic artery is usually found anteromedially to the portal vein, and it should be carefully isolated with a vessel loop and preserved. The lateral, free edge of the gastrohepatic ligament at the foramen of Winslow should be carefully inspected and palpated for an accessory or replaced right hepatic artery, which, if present, should also be isolated and protected during the subsequent resection. The GDA is isolated at its origin from the common hepatic artery and secured temporarily with a vessel loop. The continued presence of pulsatile flow in the proper hepatic artery after temporary occlusion of the GDA should be assured, both to confirm the vascular anatomy and to ensure that there is no stenosis in the proximal common hepatic artery or celiac trunk due to atherosclerotic plaque. Preliminary dissection of the plane anterior to the portal vein is begun. These measures demonstrate that there is no evidence of unresectable cancer and that the pancreatic head can be removed without concern for undue injury to the blood supply of the small intestine
and liver.

At this point, technical resectability of the pancreatic head has been assured (Fig. 71-9). The GDA is divided between clamps and is doubly tied or suture ligated. The common hepatic duct is divided just proximal to the cystic duct entry, and bile flow is controlled with a small bulldog clamp. The right gastric artery is divided between suture ligatures. For a standard pancreaticoduodenectomy, the greater omentum is divided to a point on the greater curvature of the stomach in the vicinity of the junction of the right and left gastroepiploic arteries. The lesser omentum is divided at the level of the incisura of the lesser curvature of the stomach, and the descending branch of the left gastric artery is carefully secured. If a standard pancreaticoduodenectomy is to be performed, the stomach is then divided with two firings of a linear gastrointestinal stapler. The lesser curve staple line is inverted with silk Lembert sutures. For pyloric-preserving pancreaticoduodenectomy, the duodenum is divided using a stapler approximately 2 cm distal to the pyloric ring. The ligament of Treitz is taken down with electrocautery, being certain to avoid injury to the inferior mesenteric vein. The proximal jejunum is divided approximately 15 cm distal to the ligament of Treitz with a linear gastrointestinal stapler. The distal staple line is oversewn with interrupted Lembert sutures, initially left long to use for traction and positioning of the limb during the reconstruction. The short mesojejunal vessels of the proximal segment are carefully isolated and secured close to the mesenteric border of the jejunum using fine nonabsorbable ligatures, surgical clips, or an electrosurgical vessel-sealing device. This dissection is continued proximally to the duodenojejunal junction, and then the proximal jejunum is advanced into the supracolic compartment by passing it under the superior mesenteric vessels. At this point blunt dissection is used to complete development of a tunnel between the neck of the pancreas and the SMV or portal vein. The superior and inferior pancreatic vascular arcades are then ligated on either side of the planned transection site at the neck of the pancreas using nonabsorbable suture. The neck is then divided with electrocautery. Gentle retraction of the pancreatic head, distracting it from the right lateral wall of the SMV or portal vein, helps to expose small venous tributaries from the uncinate process, which should then be carefully controlled with fine ties or suture ligatures. The first jejunal venous tributary may be quite large and is easily injured during this dissection. The uncinate branches from the superior mesenteric
artery (SMA) are then divided sequentially between clamps with great care to preserve the integrity of the SMA. The specimen is then oriented and submitted for pathological examination.

**FIGURE 71-9** Retroperitoneal dissection for pancreaticoduodenectomy. Note the ligated gastroduodenal artery (GDA), portal vein, inferior vena cava (IVC), superior mesenteric artery and vein (SMA, SMV), and the main pancreatic duct at the transected pancreas. (Reproduced with permission from Ahmad SA, Wray C, Rilo HL, et al: Chronic pancreatitis: recent advances and ongoing challenges, *Curr Probl Surg* 2006 Mar;43(3):127-238.)

The reconstruction begins with the pancreaticojejunostomy (Fig. 71-10). The jejunum is advanced through the transverse mesocolon either to the right or left of the middle colic vessels according to surgeon’s preference. Several techniques of pancreaticojejunostomy have been described. One commonly used approach is a two-layer method that is begun by placing a posterior row of interrupted nonabsorbable sutures between the pancreatic capsule and the seromuscular layer at the antimesenteric aspect of the jejunum. A small enterotomy is then made with bovie cautery across from the site of the main pancreatic duct at the pancreatic neck. An inner layer of four to eight interrupted fine absorbable monofilament sutures is used to secure the pancreatic duct to the intestinal wall at the enterotomy in a duct-to-mucosa
fashion. An anterior row of interrupted nonabsorbable suture is then used to secure the anterior pancreatic capsule to the anterior serosa at the antimesenteric border of the jejunal limb. The duct-to-mucosa anastomosis may also be performed over a 5 Fr pediatric feeding tube, which can then be exteriorized through the jejunal limb using a Witzel-type closure. The choledochojejunostomy is then constructed at a site approximately 15 cm distal to the pancreaticojejunostomy. A small enterotomy is made at the antimesenteric border of the jejunal limb at this location. The choledochojejunostomy is also performed in a duct-to-mucosa fashion, either with a single layer of interrupted absorbable monofilament suture or, if the bile duct is dilated, using absorbable continuous suture. The pancreaticobiliary limb is then secured to the transverse mesocolon using interrupted sutures, and any potential gap through which herniation may occur is closed. The retroperitoneal space at the level of the ligament of Treitz is also closed. Gastric continuity is reestablished by means of an antecolic loop gastrojejunotomy performed at a site sufficiently distal to the transverse mesocolon closure to prevent angulation of the afferent limb. A Hofmeister-type configuration is typically used, wherein the lesser curvature half of the gastric transection line is oversewn and the anastomosis is performed to the greater curvature half. The jejunal limb is oriented with the afferent limb toward the lesser curvature, efferent limb to the greater curvature. A two-layered anastomosis is preferred, with an outer layer of nonabsorbable interrupted seromuscular Lembert sutures and an inner continuous absorbable Connell-style layer. The abdomen is then irrigated with saline or dilute antibiotic solution and the abdominal wall closed. No closed suction peritoneal drains are necessary.
FIGURE 71-10 Pancreaticojejunostomy. At left, a duct-to-mucosa anastomosis is constructed using fine absorbable mattress sutures over a small (5 Fr) pediatric feeding tube. At right, the completed anastomosis, with transanastomotic stent exteriorized through the jejunum and abdominal wall to divert pancreatic secretions. (Reproduced with permission from Ahmad SA, Wray C, Rilo HL, et al: Chronic pancreatitis: recent advances and ongoing challenges, Curr Probl Surg 2006 Mar;43(3):127-238.)

BEGER PROCEDURE—TECHNIQUE

Duodenum-preserving pancreatic head resection was first described by Beger in 1972. The operation evolved from the premise that a pancreaticoduodenectomy was unnecessarily radical for benign pathology and that a more limited resection preserving the duodenum would avoid some of the adverse sequelae associated with pancreaticoduodenectomy such as delayed gastric emptying and insulin-dependent diabetes. The procedure is performed through a midline laparotomy or bilateral subcostal incision. As at the start of the pancreaticoduodenectomy, the gastrocolic ligament is separated or divided, the transverse mesocolon is mobilized off the head of the pancreas and duodenum, and a wide Kocher maneuver is performed. A cholecystectomy is performed. The GDA is isolated and divided. A tunnel is then created between the pancreatic neck and superior mesenteric vein or portal vein. The pancreatic neck is divided at this location and the pancreatic head manually rotated out of the retroperitoneum so that the cut edge faces up into the midline wound. The cystic duct is cannulated with a Bakes dilator and the CBD manually palpated in the head of the pancreas. Electrocautery is
then used to core out the head of the gland with care taken to leave a rim of pancreas attached to the duodenum and to leave the bile duct intact within that rim (Fig. 71-11). The specimen is submitted to pathology for frozen-section examination to confirm the absence of malignancy.

Pancreaticoenteric drainage is then reestablished by means of a two-sided Roux-en-Y pancreaticojejunostomy (Fig. 71-12). A Roux limb of jejunum is fashioned and advanced into the supracolic compartment through the transverse mesocolon as described for the lateral pancreaticojejunostomy. A two-layered handsewn duct to mucosa pancreaticojejunostomy is constructed at the neck margin as done for a typical pancreaticoduodenectomy, with the exception that the anastomosis is sited closer to the mesenteric margin of the jejunum. The jejunal limb is then laid such that the antimesenteric border of the limb faces the midline wound. A second long pancreaticojejunostomy is constructed here by opening the border of the jejunal limb contralateral to the first pancreaticojejunostomy at the neck for a distance appropriate to include the entire length of the proximal pancreatic rim. This pancreatic margin is then secured to the long longitudinal enterotomy by means of a single layer of interrupted nonabsorbable suture. Intestinal continuity is then reestablished by means of a jejunojejunostomy performed as described earlier for the lateral pancreaticojejunostomy. The abdomen is irrigated and closed. No closed suction drains are necessary.
FIGURE 71-11 The anatomy following transection of the neck of the pancreas and removal of the head during the Beger procedure.
FIGURE 71-12 Final anatomy of the reconstruction following a Beger procedure.

BEGER PROCEDURE VERSUS PANCREATICODUODENECTOMY—OUTCOMES

Beger has recently reviewed his three-decade experience with DPPHR for chronic pancreatitis presenting with an inflammatory mass in the pancreatic head. His perioperative results demonstrate very reasonable rates of morbidity and mortality and an impressive improvement in pancreatic pain. His pancreatic fistula rate is reported as 3.3%, the rate of delayed emptying reported is 1.5%, and perioperative mortality rate is 0.7% in 603 consecutive patients. Late outcomes reported in this series demonstrated 91.3% of patients are free of pain at a median follow-up of 5.7 years.65 There have been three randomized trials that have attempted to compare outcomes from DPPHR to those achieved with pylorus-preserving pancreatoduodenectomy (PPPD). The most widely cited is by Buchler and colleagues and has been
recently represented with long-term results. In this study 40 patients with chronic pancreatitis and a dominant focus in the pancreatic head were randomized to PPPD or DPPHR. The initial paper reported 6-month outcomes. This demonstrated a statistical advantage to DPPHR with regard to pain (75% of patients undergoing DPPHR were pain free at 6 months vs 40% of patients undergoing PPPD) and weight gain (average weight gain for those undergoing DPPHR was 4.1 kg whereas that for those undergoing PPPD was 1.9 kg). Length of hospital stay, perioperative morbidity, and perioperative mortality rates were statistically identical. The authors of this study have recently presented their long-term results. At median follow-up of 7 years, the early advantages of the DPPHR were no longer evident with patients in each group having identical health-related quality of life scores, identical pain scores, and identical rates of exocrine and endocrine insufficiency. The other randomized comparison again studied only 40 patients for 12 months. This study demonstrated statistically identical rates of pain relief but a slight statistical advantage in terms of scores seen on a general assessment of health-related quality of life for patients undergoing DPPHR relative to those undergoing PPPD. More recently, the group from Freiburg reported short- and long-term results from the third randomized trial comparing DPPHR including both Beger and Frey operations to PPPD. This study randomized 85 patients (43 to PPPD and 42 to DPPHR) and reported follow-up over 5 years. Postoperative quality of life was assessed by the EORTC QLQ-30 instrument. The authors noted a significant saving in operative time for DPPHR versus PPPD (360 minutes vs 435 minutes) but no differences in rates of postoperative morbidity, mortality, or long-term quality of life, pain control, and endocrine or exocrine function.

**FREY PROCEDURE—TECHNIQUE**

The disadvantage of the DPPHR as described by Beger is that it does not address disease (either diffuse parenchymal fibrosis with side branch disruption or strictureing with upstream dilation of the main pancreatic duct) that may coexist in the pancreatic body and tail. Late failures of the Beger procedure have been attributed to poor drainage of the pancreatic body and tail. In an effort to overcome this, and in large part to avoid the certain exocrine and endocrine insufficiency that comes with the near-total pancreatectomy pioneered by one of his early mentors, Frey and colleagues
developed a procedure that combines a duodenum-preserving pancreatic head resection with a hybrid resection or drainage procedure at the pancreatic body and tail (referred to as a local resection of the pancreatic head with longitudinal pancreaticojejunostomy [LR-LPJ]) (Fig. 71-13). In this procedure, no tunnel is created behind the pancreatic neck. Instead, the entire length of the pancreas is exposed anteriorly. The GDA is ligated. The gallbladder is removed. The cystic duct is cannulated using a Bakes dilator and the bile duct is identified in its course through the head of the pancreas by palpating the dilator. The pancreatic head is then excavated down to the level of the portal vein, with care taken to leave a rim of tissue surrounding the bile duct at the duodenal margin. From this cavity an extensive longitudinal unroofing of the pancreatic duct through the body and tail is made using electrocautery. If the duct is not dilated in the tail, then the body and tail may simply be excavated as done at the pancreatic head (Fig. 71-14). Pancreaticoenteric drainage is then accomplished by means of a lateral pancreaticojejunostomy covering the entire excavation cavity, typically constructed using a Roux-en-Y jejunal limb sewn to the pancreatic capsule in one or two layers.
FIGURE 71-13 Cross-sectional drawing of the pancreas following coring of the pancreatic head during a Frey procedure.
FREY PROCEDURE VERSUS BEGER PROCEDURE—OUTCOMES

In various reports including small randomized trials, the results of LR-LPJ appear similar to those reported for the Beger DPPHR, with postoperative mortality less than 1% and morbidity reported as 19% to 32%. Excellent pain relief is obtained in about 75% of patients and the change in postoperative pain scores and rates of postoperative exocrine and endocrine insufficiency are identical over follow-up as long as 9 years. A small prospective randomized trial compared LR-LPJ to PPPD with an average length of follow-up of 2 years. None of the published evaluations of pancreatic surgery for pancreatitis grade perioperative morbidity, and it is difficult to truly gauge the relatively complicated profiles for the various procedures available to manage chronic pancreatitis; however, the hybrid procedures generally seem to be less morbid than pancreaticoduodenectomy. In the small prospective trial comparing Frey to PPPD, postoperative morbidity was significantly higher in the PPPD group compared to LR-LPJ (30% vs 17%). Although there was similar improvement in pain symptoms, the LR-LPJ group demonstrated a statistically better overall quality of life as measured by a general assessment of health-related quality of life. Long-term results of the study were published in 2008 with a median follow-up of 7 years. At that length of follow-up, there were no statistical differences with regard to the improvement in pain, health-related quality of life, or the incidence of exocrine or endocrine insufficiency. More recently the group has presented 15-year outcomes for 32 patients undergoing PD and 32 patients undergoing Frey procedure. At this time point, pain control was comparable between the cohorts but the group of patients managed with the Frey procedure demonstrated statistically better quality of life scores as measured by the EORTC QLQ C30 instrument. Patients undergoing Frey procedure demonstrated scores of 100 in physical status and working ability domains, whereas those undergoing PPPD demonstrated scores of 60 in the physical status domain and 50 in working ability domain.

BERNE PROCEDURE—TECHNIQUE AND OUTCOMES
There has been one further modification of the Beger DPPHR made in recent years. The Berne procedure adopts the technical safety advantage of the Frey LR-LPJ that comes by avoiding transaction of the neck of the pancreas off the portal vein. In this modification, as in the Beger DPPHR, no lateral pancreaticojejunostomy is performed. The anterior surface of the mass in the head is palpated and then cored out by electrocautery. A Roux limb is then sewn to the residual pancreatic rim at this location. One randomized trial comparing the Berne modification to the standard Beger DPPHR showed rough equivalence of outcomes with these procedures. One more recent publication has reported the results of retrospective evaluation of 160 patients managed by the Berne procedure with mean follow-up of 5.3 years (range 0.5 to 10 years). This represents one of the largest series reported on surgical management of chronic pancreatitis. The results demonstrate preserved endocrine function relative to preoperative functional tests, and significant and durable improvement in the amount of pain experienced and in quality of life relative to preoperative scores using the EORTC QLQ C30 instrument.

**Small Duct Disease or Diffuse Sclerosis**

In many instances, as the disease progresses there will be no dominant focus of ductal obstruction and no dominant mass. Instead, the morphology of the disease is characterized by diffuse calcification and/or diffuse fibrosis with atrophy of the pancreatic parenchyma. In these cases the pancreatic remnant may be quite small and will have a uniform firm consistency. Patients with this morphology of disease present a particular challenge, as there is no discrete target for either endoscopic or surgical intervention. Those manifesting intractable pain syndromes have had, until very recently, few and imperfect options for surgical management. These have included total or near-total pancreatectomy procedures that have traditionally been avoided due to the significant morbidity associated with profound postoperative exocrine and endocrine insufficiency.

Autologous islet transplantation may mitigate the diabetic consequences of total pancreatectomy. The first human autologous islet transplant was performed at the University of Minnesota in 1977. Since that time, several hundred procedures have been reported from Minnesota, Miami, Cincinnati, Leicester, and other emerging centers. Taken together, the results from
these institutions suggest that in highly selected patients, complete pain relief (without the use of narcotics) and insulin independence can be achieved but that there is a significant rate of recidivism of pain after 1 year of follow-up. Although reports of assessment of quality of life after total pancreatectomy with autologous islet transplantation suggest that the procedure compares favorably to either total pancreatectomy without islet transplantation or to continue nonoperative management of pain, compelling evidence comparing this approach to alternative therapies in appropriately matched controls is lacking. Total pancreatectomy with autologous islet transplantation is costly and requires a high degree of technical expertise that is difficult to replicate. The indications for islet autotransplantation remain controversial and the overall safety and efficacy of the procedure have not been fully validated outside a handful of centers. Questions regarding the long-term viability of the islets and adverse impact on the surrounding liver parenchyma have been raised. Pathologic analysis of liver tissue that has been explanted following islet transplant has demonstrated that the transplanted islets typically migrate across the liver sinusoids and reside in the liver parenchyma. It has also been noted that the transplanted islets exhibit some degree of peri-islet fibrosis in the liver. There have been no reports of chronic hepatic fibrosis or cirrhosis in patients receiving autologous islets, but the concern exists. Complete long-term insulin independence is achieved only in a relatively small minority of patients after islet autotransplantation and that pain is persistent or recurrent in about half of patients even after total pancreatectomy. Currently, the strongest arguments in favor of total pancreatectomy and islet autotransplantation can perhaps be made in the setting of a limited subset of patients with hereditary pancreatitis, who otherwise carry a significant long-term risk of developing pancreatic cancer. When a more traditional surgical operation (resection or drainage) is also possible in this setting, decision-making must be highly individualized (Fig. 71-15).
FIGURE 71-15  Hereditary chronic pancreatitis associated with \textit{PRSS1} gene mutation. A single calcification is evident in the pancreatic head, and the main pancreatic duct shows diffuse dilation. Lateral pancreaticoduodenectomy is an appropriate surgical option; total pancreatectomy with islet autotransplantation to eliminate cancer risk associated with hereditary pancreatitis is controversial.

**TOTAL PANCREATECTOMY WITH AUTOLOGUS ISLET TRANSPLANTATION—TECHNIQUE (TPAIT)**

Total pancreatectomy is performed as either an en bloc resection of the pancreatic head, body, and tail or, more commonly, in a staged fashion with a left pancreatectomy followed by a head resection (pancreaticoduodenectomy) allowing initial islet processing on the body and tail specimen. The isolation process relies on enzymatic and mechanical mechanisms to dissociate the islets from surrounding acinar tissue and fibrosis. Depending on the proximity of the islet isolation facilities and the efficiency of the process,
infusion of the islet preparation into the portal circulation may be performed
during the same anesthetic or postoperatively (usually the same day) under
radiological guidance. Briefly, the resected pancreas is cooled to 4°C in an
organ-preserving solution (eg, University of Wisconsin Solution). The
pancreas is then transected at the neck of the gland and the pancreatic duct
cannulated. The ductal system is then perfused with a cold solution of the
purified digestive enzyme collagenase. The gland is sectioned and then
physically shaken in a small digestion chamber at 37°C. The digestion of the
gland is monitored continuously by means of a microscopic examination of
samples of the digestate taken throughout the process. The digestion is
continued until the acinar tissue is separated from the islets but stopped
before the islets begin to fragment. The islets are then partially purified from
the acinar debris by gradient density centrifugation on a cold dextrose
gradient. The islets are washed and resuspended in an albumin-rich transplant
medium or cultured. The islets are transplanted by direct injection into portal
circulation, with access to the portal circulation being achieved under
ultrasound-guided percutaneous placement of a transhepatic portovenous
catheter in interventional radiology or by direct operative cannulation of the
portal vein.

AUTOLOGOUS ISLET TRANSPLANTATION—OUTCOMES

Several recent publications have demonstrated the efficacy of autologous
islet transplantation in both adult and pediatric populations. In general, short-
and long-term outcomes in selected populations of adults have been
favorable. One recent publication from the University of Cincinnati reported
outcomes from 166 patients undergoing TPAIT and having 5 years of follow-
up. At the 5-year mark, 74% of patients were narcotic-independent. All
patients demonstrated stable glycemic control and 27% demonstrated long
term insulin independence. These results are consistent with previous
publications on long-term results from TPAIT from the University of
Minnesota. Such successes of TPAIT in adult populations have been
encouraging, and prompted groups doing the procedure to apply the
technology to adolescents with severe early manifestation of hereditary foms
of chronic pancreatitis. In general, TPAIT in these young people has been
reported to be safe, with morbidity profiles and functional results similar to
those found in adult populations undergoing TPAIT in the same centers.
The technology has also been effectively employed as salvage therapy for patients with symptoms refractory to more well-established resection and drainage procedures. The group from Cincinnati has recently presented a series of 64 patients undergoing completion total pancreatectomy with islet auto transplantation (CPIAT) following an initial operative intervention (either pancreaticoduodenectomy, Frey, Puestow, or Berne procedure). Follow-up was only short-term, but islet yields were reasonable given the fact that there had been a prior partial pancreatectomy in most cases. Nearly half (44%) of patients achieved narcotic independence. Twenty percent of patients achieved insulin independence, and quality of life as assessed by the SF-36 metric was improved in all domains.\textsuperscript{81}

**CONCLUSIONS**

Chronic pancreatitis is a relapsing inflammatory process that results in a variable degree of parenchymal destruction and fibrotic change in the pancreas, with consequent clinical manifestations typically including characteristic abdominal pain, and exocrine and endocrine insufficiency. A single unifying model for the pathogenesis of chronic pancreatitis remains elusive, although recent basic and clinical research has identified a number of gene mutations, immunologic conditions, environmental toxins, and anatomic anomalies that alone and together confer risk of developing chronic pancreatitis. The morphology of pathological change seen in the gland at the time that patients present for treatment varies significantly from one patient to the next. A myriad of endointerventional and surgical procedures have been developed over time and are now applied in the treatment of the disease. Both the endoscopic and surgical procedures used are technically demanding and carry substantial risk of morbidity. While there is substantial retrospective case-series evidence demonstrating the utility of these approaches in well-selected patients, high-level evidence comparing the efficacy of the interventions in large series is lacking. For all of these reasons, chronic pancreatitis is often best managed in experienced centers in which multidisciplinary teams collaborate to individualize treatment in the context of established local expertise with various medical, endoscopic, and surgical therapies.
REFERENCES


INTRODUCTION

The collective phrase “cystic lesions of the pancreas,” typically described on cross-sectional imaging of the abdomen, refers to any cystic neoplasms of the pancreas and/or other cystic lesions, many of which cause “cyst-like” dilatations of the main or side branch pancreatic ducts. Specifically, the descriptor “cystic neoplasms of the pancreas” encompasses a wide variety of pathologic entities of the pancreas with variable malignant potential. The incidence of these cystic neoplasms seems to increase with age, with one autopsy study demonstrating that up to a quarter of elderly individuals harbor cystic lesions of the pancreas at their demise. As the use of abdominal computed tomography (CT) and magnetic resonance imaging (MRI) is increasing, cystic lesions of the pancreas are being defined more frequently, with the majority asymptomatic at discovery. Laffan and colleagues in 2008 estimated the incidence of asymptomatic discovered cysts on abdominal imaging for unrelated diagnoses at 2.6%. Some of these lesions will be malignant or have malignant potential at diagnosis, while others are clearly
benign and may not warrant further surveillance. Resection of benign cystic pancreas lesions or those containing only high-grade dysplasia (premalignant) leads to nearly universal survival, while surgery for invasive carcinoma associated with cystic neoplasms generally has a more favorable prognosis than the results for resection of typical pancreatic ductal adenocarcinoma.\textsuperscript{5-7} Thus, careful consideration must be given to the diagnosis and prognostic implications of these lesions. As more becomes known about these neoplasms, the treatment and observation algorithm will continue to evolve to minimize unnecessary interventions, while maximizing the impact of surgical treatment.

An ideal diagnostic approach would allow for the resection of only those lesions with concurrent or near-future risk of malignancy, while excluding from surgery those individuals with either nonenlarging benign lesions or a prohibitive operative risk, thus minimizing the potential occurrence of mortality and morbidity associated with the surgical treatment of these cystic lesions. Recent advancements in imaging by CT, MRI, and endoscopic ultrasonography (EUS), linked with refinements in the pathological, molecular, and genetic understanding of cystic neoplasms of the pancreas, have furthered this effort. History and clinical criteria, such as age, gender, presence of symptoms, location of the neoplasm within the pancreas, as well as morphology by cross-sectional imaging and cyst fluid analysis by EUS with fine-needle aspiration (EUS-FNA), all may play a role in the diagnosis of pancreatic cystic neoplasms and assessment of the need for resection. While the phrase “cystic neoplasm of the pancreas” encompasses a large variety of pathologic entities, this review will focus on the most commonly encountered that may require surgical intervention.

The most common non-neoplastic cysts of pancreas are typically considered to be pancreatic pseudocysts (or early post-pancreatitis acute fluid collections). Their diagnosis is aided (and typically confirmed) by a history of acute or chronic pancreatitis.\textsuperscript{8} Congenital cysts are rare and include those associated with genetic diseases such as autosomal dominant polycystic disease,\textsuperscript{9} cystic fibrosis,\textsuperscript{10} and von Hippel–Lindau (VHL) disease.\textsuperscript{11,12} Lymphoepithelial cysts are rare benign lesions of the pancreas lined with squamous epithelium.\textsuperscript{13} Peripancreatic cystic lesions (such as esophageal or intestinal duplication cysts) may be mistaken for true pancreatic cystic lesions and need to be within the differential diagnosis in select situations.\textsuperscript{14} Finally,
solid pseudopapillary neoplasms (which may have cystic components) are rare lesions occurring predominantly in young women, for which resection of the primary tumor results in an excellent opportunity for cure.

Three lesions make up approximately 90% of the cystic neoplasms seen in the pancreas: serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs). Overall, these three common pancreatic cystic neoplasms can be classified as either “mucinous” or “non-mucinous,” a distinction that has important clinical significance. SCNs (nonmucinous lesions) rarely demonstrate a progression to malignancy. Unequivocal proof of a SCN may permit nonoperative management of these lesions, provided symptoms do not mandate resection. Although the majority of non−mucin-producing lesions are benign in nature, cystic “degeneration” of other pancreatic tumors (ie, endocrine, solid pseudopapillary, or ductal adenocarcinoma) does occur and must be considered in the workup, as these may necessitate surgical resection. Mucin-producing lesions of the pancreas can be segregated into two types, which may differ significantly in natural history. Restriction of the definition of MCNs to include only those lesions with subendothelial ovarian-type stroma has permitted an improved distinction between MCNs and IPMNs. Consensus guidelines developed (and recently revised) by the International Association of Pancreatology (“Sendai” and “Fukuoka” guidelines) may assist in the management of cystic neoplasms of the pancreas. The premalignant nature of MCNs (and most IPMNs) prompts resection in patients who are acceptable operative risks, while observation of some branch duct IPMNs may be tenable, with an eventual risk of malignancy less than the operative mortality of pancreatic resection.

PATHOLOGICAL CLASSIFICATION

The accurate pathological description of pancreatic cystic neoplasms has evolved significantly in the past several decades, influenced largely by an improved understanding of the malignant potential of MCNs in comparison to the largely benign nature of SCNs, and the emergence of an understanding of the pathogenesis and behavior of IPMNs. Current classification of these tumors follows the World Health Organization (WHO) International Classification of Tumors as published in 2010 (Table 72-1). While the
diagnostic criteria and organizational schema for these tumors are likely to be adapted further in future editions, the current classification system provides a means to stratify these tumors in terms of prognosis and management. In this review, particular attention will be paid to the three most common lesions: SCNs, MCNs, and IPMNs (Table 72-2). Although this chapter is organized by pathologic diagnosis, the actual workup and treatment of these cystic lesions of the pancreas may have significant overlap, as at times the diagnosis may be challenging to delineate until definitive surgical resection.

### Table 72-1: World Health Organization International Classification of Tumors, 2010—Cystic Neoplasms of the Pancreas

<table>
<thead>
<tr>
<th>Serous cystic neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma</td>
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<tr>
<td>Serous microcystic adenoma</td>
</tr>
<tr>
<td>Serous oligocystic adenoma</td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucinous cystic neoplasms</th>
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</thead>
<tbody>
<tr>
<td>Mucinous cystic neoplasm with low- or intermediate grade of dysplasia</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm with high-grade dysplasia</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm with an associated invasive carcinoma</td>
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<table>
<thead>
<tr>
<th>Intraductal papillary mucinous neoplasm</th>
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</thead>
<tbody>
<tr>
<td>Intraductal papillary mucinous neoplasm with low- to intermediate-grade dysplasia</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm with high-grade dysplasia (noninvasive)</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm with an associated invasive carcinoma</td>
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</tbody>
</table>

### Table 72-2: Common Cystic Neoplasms of the Pancreas
SEROUS CYSTIC NEOPLASMS

SCNs, previously referred to either as serous cystadenomas, glycogen-rich adenomas, or microcystic adenomas, are almost always benign. Careful delineation of the radiological and clinical features that distinguish these lesions may support and facilitate nonoperative management of these lesions when appropriate (Table 72-2).

Pathological Features

The majority of SCNs are polycystic or so-called “microcystic adenomas,” typically characterized by a well-circumscribed, soft mass which includes numerous small cysts filled with clear serous fluid arranged in a characteristic honeycomb-like pattern. Larger cysts may line the periphery of the lesion. The multiple small cystic loculations are well defined and are often accompanied by a central stellate scar with or without calcifications. These

**Table 72-2:**

<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>Gender (Ratio F:M)</th>
<th>Age Range</th>
<th>Gross Feature</th>
<th>Microscopic Features</th>
<th>Imaging Features</th>
<th>Fluid Analysis</th>
<th>Malignant Potential</th>
<th>Suggested Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystic neoplasm (SCN)</td>
<td>F &gt; M (7:3)</td>
<td>60-80 years</td>
<td>Typically polycystic “microcystic” with central stellate scar, may be oligocystic</td>
<td>Clear-cystic, single-layer cuboidal epithelium, glycogen-rich cells</td>
<td>Microcystic, honeycomb pattern with central stellate scar</td>
<td>Low viscosity, clear glycogen rich cystoplasm</td>
<td>Almost uniformly benign</td>
<td>Stable size and asymptomatic surveillance</td>
</tr>
<tr>
<td>Macinuous cystic neoplasm (MCN)</td>
<td>F &gt; M (10:1)</td>
<td>Perimenopausal - 40-50 years</td>
<td>Large, macrocystic, solitary, thick-walled</td>
<td>Subendobdial oval/circular stroma, tall columnar mucin producing epithelium</td>
<td>Macrocystic lesion in the body or tail without communication to ductal system, peripheral calcifications</td>
<td>High viscosity, elevated CEA, low amylose</td>
<td>Potentially malignant (exhibit spectrum from adenoma to carcinoma)</td>
<td>Asymptomatic and size ≤ 3 cm: surveillance or observation (after patient education)</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm (IPMN)</td>
<td>F = M (1:1)</td>
<td>60-70 years</td>
<td>Multilocular, involve main pancreatic duct and/or branch ducts</td>
<td>Tall columnar mucin producing epithelium with variable degrees of dysplasia</td>
<td>Main duct IPMN: diffuse or segmental main pancreatic duct dilation</td>
<td>High viscosity, elevated CEA Elevated amylose</td>
<td>Potentially malignant (exhibit spectrum from adenoma to carcinoma)</td>
<td>Asymptomatic and size ≤ 3 cm: resect Symptomatic resect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Branch duct IPMN: pancreatic cyst with communication to ductal system</td>
<td>Mixed type IPMN: combination of cyst with communication to ductal system and main duct dilation</td>
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<td></td>
<td></td>
<td></td>
<td>Branch duct IPMN: resect if symptomatic, tumor &gt; 3 cm, mural nodules, positive cytology, rapid growth, main duct dilatation or young and healthy (age &lt;55 years)</td>
<td>Observe, if asymptomatic, tumor &lt;3 cm, no mural nodules, negative cytology, stable size, normal main duct, and advanced age (&gt;75 years)</td>
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</table>
features may be highly suggestive of an SCN when seen on CT or MRI (Figs 72-1 and 72-2). A small number of SCNs (≤10%) are oligocystic adenomas and present with one or more dominant cysts rather than multiple conjoined microcysts. Rarely, a single dominant cystic lesion may be identified. These unusual SCNs may be more difficult to distinguish radiographically from MCNs, IPMNs, pseudocysts, and other cystic lesions.

FIGURE 72-1 This CT image depicts a cystic neoplasm in the head and neck of the pancreas (small arrow) detected incidentally in a 75-year-old man undergoing evaluation for nephrolithiasis. The patient underwent a pylorus-preserving pancreaticoduodenectomy without complications. Final pathology revealed a 6-cm serous cystic neoplasm without evidence of malignancy.
FIGURE 72-2  A. Abdominal CT (axial image) of a 61-year-old woman who presented with pruritus and jaundice and was found to have a large cystic lesion in the head of the pancreas (arrow). B. On coronal CT image, this polycystic mass with central calcifications (arrow) abuts the proximal superior mesenteric vein (SM) and portal vein (PV), and was resected via a pylorus-preserving pancreaticoduodenectomy for complete resection. Final pathology revealed a benign serous cystic neoplasm.

Beyond these gross distinctions, both microcystic and oligocystic adenomas are composed of a single layer of simple cuboidal epithelium with rounded nuclei and clear cytoplasm which is glycogen rich and stains periodic acid-Schiff-positive (Fig. 72-3). The cystic fluid is serous (clear) and typically has no mucin content, with a low carcinoembryonic antigen (CEA) level (< 5 ng/mL), factors that may provide diagnostic information upon cyst aspiration. Cytology diagnostic for SCN is present in less than 50% of cases; however, when positive the sensitivity is high.

FIGURE 72-3  Photomicrograph of a typical SCN of the pancreas. Characteristic features include the single layer of cuboidal epithelial cells lining the microcysts within the lesion, uniform round nuclear architecture,
and clear cytoplasm. The cyst cavities contain serous fluid and little cellular debris.

The malignant potential of SCN is so low that most experienced centers recommend management of these lesions as benign entities. Certainly the argument can be made that a clearly documented classic-appearing SCN need not be resected unless symptomatic or enlarging. The incidence of serous cystadenocarcinoma is extremely low, and although the WHO has given serous cystadenocarcinoma a distinct definition, data on this extremely rare lesion are scarce. The WHO requires evidence of distant metastasis to verify the diagnosis. To date, there have been 42 cases of “invasive” or metastatic serous cystic neoplasms reported in the literature, with Reid et al. recently performing a critical analysis of these cases, finding that most would no longer be considered as serous “cystadenocarcinoma” based on the WHO 2010 classification. Khashab and colleagues reviewed the Johns Hopkins Hospital experience with 257 resected serous cystic neoplasms. Of these 257 cases, fourteen patients had “aggressive” tumors (defined as local extension or invasion), with two of these cases having liver metastases (considered malignant). The authors found that tumor size and location in the head of the pancreas are independent risk factors for aggressive behavior. Evidence of distant metastatic disease is considered necessary to confirm the rare diagnosis of serous cystadenocarcinoma according to the WHO, as both the primary and extrapancreatic disease may appear histologically indistinguishable from benign SCN. Importantly, vascular and perineural invasion, or local invasion of the stomach and duodenum, are not sufficient criteria for the diagnosis of malignancy of SCN. Hence, true histologic malignancy in the setting of serous cystic neoplasms is exceedingly rare.

**Clinical Presentation**

SCNs occur predominately in women in the sixth decade of life, while men tend to present at a later age. Bassi and colleagues described 100 patients with SCN, 87 of whom were female, with a mean age at presentation of 52 years. The average age of the 13 male patients was 54 years. In another study from the Massachusetts General Hospital, 75% patients were women, and the female patients were significantly younger at presentation than were
the men (60 vs 67 years, \( p = .018 \)). In the recent review of 257 cases from the Johns Hopkins Hospital, 179 patients were female, with a mean age of 61 years.

The majority of patients with SCN are asymptomatic. When symptoms exist, abdominal pain is the most common presenting symptom, weight loss is seen in 14 to 22\% of patients, and fewer patients (10\%) present with a mass or fullness. Symptoms typically associated with invasive disease, such as jaundice (6\%) or pancreatitis, are uncommon (Fig. 72-2). Nausea and vomiting related to compression of the upper gastrointestinal tract may occur in 7\% to 10\% of patients. Traditionally, SCNs have been described as having a predilection for the pancreatic body and tail, although Le Borgne and coworkers described a relatively even distribution throughout the gland in 170 lesions (38\% head, 41\% body, 20\% tail). Khashab et al. reported 39\% of SCN in the pancreatic head, 21\% in the body, 31\% in the tail, and 9\% were considered “extensive.” Large SCNs located in the head are surprisingly unlikely to cause biliary or duodenal obstruction, reflecting their slow pattern of growth, soft texture, and lack of invasive behavior. Rarely, extremely large tumors have been seen in elderly patients, with considerable symptoms of abdominal fullness and occasionally gastroduodenal obstruction or jaundice.

One clinical condition that has been clearly associated with SCNs of the pancreas is the VHL syndrome. Simple pancreatic cysts or SCNs occur in 17\% to 56\% of patients with this heritable multisystem neoplastic syndrome. The VHL tumor suppressor gene is located on chromosome 3p25. Vortmeyer et al. demonstrated deletion of 3p25 in 7 of 10 sporadic SCN cases studied, suggesting a role for the VHL gene in SCN tumorigenesis, even in the absence of the VHL syndrome. A recent review of 23 patients with VHL syndrome operated on for nonfunctioning pancreatic neuroendocrine tumors described that 13 (57\%) of those patients had associated SCNs of the pancreas.

**Diagnosis**

SCNs often have a characteristic imaging phenotype (see Figs 72-1 and 72-2). Most are well-demarcated solitary multicystic masses composed of innumerable small cysts. Up to one-third have a central, calcified starburst
SCNs may also present as oligocystic or unilocular cystic lesions, making differentiation from other cystic lesions of the pancreas difficult. Lee and colleagues reported on the preoperative diagnostic accuracy of CT in pathologically confirmed SCN. Radiological features led to a correct diagnosis in only 36% of unilocular SCNs, while honeycombed microcystic and multilocular macrocystic SCNs were appropriately defined in 81% and 88%, respectively \((p = .005)\). Overall in their series, CT diagnosis was accurate in 71% of SCNs. In 164 patients with surgically verified pancreatic cystic lesions, 28 of whom had a SCN, Shah et al. suggested that the CT features predictive of the diagnosis of SCN are microcystic appearance \((22/28, 78\%)\), surface lobulations \((25/28, 89\%)\), and central scar \((9/28, 32\%)\). Stepwise logistic regression analysis showed that only a microcystic appearance was predictive for the CT diagnosis of SCN \((p = .0001)\). MRI correctly predicted the pathological diagnosis of SCN with greater frequency than did CT in the study by Bassi and coworkers. CT allowed for the correct diagnosis in 54%, incorrect diagnosis in 34%, and was nondiagnostic in 12% of SCNs. The results with MRI were 74%, 26%, and 0%, respectively. A recent study by Chu and colleagues using pancreas protocol CT imaging in resected SCNs revealed that only 20% of cases had the “classic appearance” of multilocular masses with central stellate scars and calcifications. CT attenuation was helpful in distinguishing SCNs from MCNs, IPMNs, pseudocysts, and insulinomas, but not pancreatic ductal adenocarcinoma. The presence of external lobulations and the absence of “aggressive” features (such as pancreatic duct dilation, vascular invasion, lymphadenopathy, and liver metastasis) were helpful in distinguishing between SCN and classic pancreatic ductal adenocarcinoma.

The limitations of the radiological diagnosis of SCN may call for additional analysis, which is frequently sought by EUS-FNA with cyst fluid cytology and biochemical analysis. The risk of complications with EUS-FNA is relatively low. Cyst fluid aspirates from SCN are frequently sparsely cellular and may be contaminated with columnar enterocytes and mucin from the scope and needle traversing the gastric or intestinal mucosa, potentially clouding the diagnostic accuracy of cytology. Cytology alone was found to be diagnostic of SCN in only 7 of 21 cases studied by Huang and others from MD Anderson Cancer Center. Detection of intracytoplasmic glycogen was noted to enhance the diagnostic confidence for the diagnosis of SCN.
Cyst fluid analysis is an additional adjunct (beyond cytology) to improve the diagnostic accuracy of EUS-FNA. Fluid from within an SCN is typically low in viscosity and amylase due to a consistent lack of connection to the pancreatic ductal system. CEA levels less than 5 ng/mL have a sensitivity of 54% to 100%, and specificity of 77% to 86% in the differentiation of SCN from other pancreatic cystic lesions. The finding of a cyst fluid carbohydrate antigen (CA) 19-9 level less than 37 U/L and a CEA less than 5 ng/mL virtually excludes an MCN or IPMN.

Allen et al. reported on the analysis of cyst fluid using a biomarker panel developed for pancreatic cancer. Assessment of protein expression within the cyst fluid led to an error rate in classification of lesions of 27% when all three types of cystic neoplasms were evaluated (SCN, MCN, and IPMN). When limiting the analysis to separating SCN from IPMN, this method had an error rate of only 8%, compared with a 14% error rate with the use of CEA levels alone. The greatest utility of protein expression analysis might be in the differentiation of cystic lesions of the head of the pancreas, as the vast majority of MCNs occur in the body and tail of the pancreas. However, the cost of this method may not be justified by the relatively small improvement in diagnostic accuracy. In addition, Cao and colleagues recently studied a three-marker panel of glycoforms of MUC5AC and endorepellian and showed 89% sensitivity and 100% specificity in distinguishing between mucinous (MCN, IPMN) and nonmucinous (SCN, pseudocysts) cystic neoplasms of the pancreas. Recently, Springer and colleagues examined a combination of molecular and clinical markers from a multi-institutional collaboration of resected cystic neoplasms of the pancreas and identified a combination of markers that approach 100% sensitivity and 98% specificity in diagnosing SCNs. The combination of the clinical characteristics of patients >25 years of age without abdominal pain or evidence of communication of the cyst with the pancreatic ductal system and the molecular presence of a VHL mutation and/or loss of heterozygosity of chromosome 3, as well as the absence of KRAS, GNAS, and RNF43 mutations, allowed for excellent diagnostic power.

**Treatment**

Observation of patients with SCN may be appropriate in asymptomatic
patients. When a secure diagnosis of SCN is made, modern series demonstrate that a growing number of SCNs are being kept under surveillance by serial imaging (Table 72-2). Typically a pathological diagnosis is not required when classic imaging characteristics are observed. Bassi and colleagues followed 32 patients with the diagnosis of SCN for a median time of 69 months, without any observed development of malignancy or significant increase in diameter of the lesion. Rapid rate of growth of a lesion may heighten suspicion for the development of malignancy or increase the likelihood of developing symptoms. In a report from the Massachusetts General Hospital, Tseng and coworkers found a more rapid rate of growth in SCNs greater than or equal to 4 cm in size at presentation, compared with smaller tumors (1.98 cm/yr vs 0.12 cm/yr, \( p = .0002 \)). Tumors less than 4 cm were less likely to be symptomatic than were those greater than or equal to 4 cm (22 vs 72%, \( p < .001 \)). Resection was thus suggested by these authors, even for asymptomatic SCNs that were greater than or equal to 4 cm. A recent multinational review of over 2600 SCNs revealed that the average tumor size of patients who underwent surgical resection was 40 mm, with the most common indication being an “unclear diagnosis.” Only three serous cystadenocarcinomas were encountered in this entire cohort.

When the diagnosis of SCN is uncertain, pancreatic resection is most often performed according to oncological principles, as if the lesion was malignant or had malignant potential (Fig. 72-2). Standard procedures include distal pancreatectomy for lesions of the body or tail, or pancreaticoduodenectomy for right-sided lesions. This practice avoids performance of an inadequate cancer operation in cases in which a malignancy is found on final pathological analysis. However, if the diagnosis of SCN is confirmed preoperatively, a less radical approach may be considered. Enucleation of SCNs has been shown to be technically feasible, although it can be challenging and is associated with a significant risk of pancreatic fistula. A central pancreatectomy, with remnant pancreatic reconstruction being performed via pancreaticogastrostomy or Roux-en-Y pancreaticojejunostomy (PJ), may be considered in select patients with lesions of the pancreatic neck. Distal pancreatectomy with splenic preservation may also be considered, particularly for small lesions in the tail, where the splenic hilum is more easily dissected. Lesions in the head of the pancreas that are not amenable to enucleation are best treated with pylorus-preserving pancreaticoduodenectomy. Many patients undergoing
pancreaticoduodenectomy will have an otherwise normal pancreas, hence meticulous attention must be paid to the technique of PJ, since such patients have a significantly higher risk for developing a pancreatic fistula related to a failure of healing at the PJ. There has been some enthusiasm for duodenum-preserving pancreatic head resection as well, although this procedure has not had widespread application. The use of minimally invasive techniques is encouraged in institutions with experience and training in these complex procedures. Patients with pathologically proven, completely resected SCNs do not require serial imaging in follow-up. Recommendations for appropriate monitoring of unresected SCNs vary, but serial imaging with either CT or MRI every 6 months for 2 years and then annually or every other year thereafter seems reasonable.

**MUCINOUS CYSTIC NEOPLASMS**

Progress in the diagnosis and management of pancreatic cystic neoplasms has been aided in large part by the recognition of distinct pathological features that distinguish MCNs from other cystic lesions. The distinction between MCN and SCN is critical, as the premalignant and malignant behavior of MCNs stand in stark contrast to the nearly universally benign nature of SCNs. Many of the same diagnostic challenges that exist for SCNs are true for MCNs, but the management decisions may be quite different, due to the differing clinical phenotype of these lesions.

While the true prevalence of MCNs is difficult to identify, more recent series suggest that approximately 15% to 30% of cystic neoplasms of the pancreas are MCNs. However, our experience at the Thomas Jefferson University Hospital reflects a lower percentage. Clinical series published prior to the establishment of the diagnostic criteria for IPMN in 1996 likely overestimated the relative prevalence of MCNs in comparison to other cystic lesions, since they included what are now categorized as IPMNs as various “mucinous tumors.”

**Pathological Features**

MCNs (Table 72-2) are typically spherical, thick-walled, septated or unilocular cysts with a tall columnar mucin-producing epithelium
accompanied by a subendothelial ovarian-type stroma that appears as a dense layer of spindle cells with sparse cytoplasm and uniform, elongated nuclei (Fig. 72-4). This stroma regularly expresses progesterone receptors, and less frequently estrogen receptors, and over 60% of these stroma stain for human chorionic gonadotropin. Both the WHO and the Armed Forces Institute of Pathology (AFIP) have defined the presence of this ovarian-like stroma as a requirement for the diagnosis of an MCN. The original and updated International Consensus Guidelines (“Sendai” and “Fukuoka”) for the management IPMN and MCN have also required the presence of ovarian-type stroma as a necessary criterion for the diagnosis of MCN, so as to prevent the misclassification of IPMN as MCN. In addition, MCNs typically do not communicate with the pancreatic ductal system, and this serves as another distinction between IPMNs. Given the similarity of the histology and immunohistochemistry between MCNs and ovarian mucinous cystadenomas, MCNs have been postulated to arise from ovarian rests (or ovarian-like stem cells) within the pancreas.

FIGURE 72-4 MCNs of the pancreas are distinguished by a uniform columnar epithelium (top) associated with a dense underlying ovarian-like stroma (bottom).

MCNs exhibit characteristics of an adenoma-carcinoma sequence.
Dependent on the degree of atypia, they are classified as mucinous cystadenomas, mucinous cystic tumors (borderline lesions), in situ lesions (high-grade dysplasia), or invasive cystadenocarcinomas (mucinous cystadenocarcinomas). Atypical changes within the lining epithelium may be patchy and sparse, with abrupt transitions to normal mucosa. Classification of MCN should be based upon the highest degree of atypia present, and the entire lesion should be examined pathologically. Invasive carcinomas arising within MCNs are usually tubular or ductal type, although some may be undifferentiated carcinoma with osteoclast-like giant cells, adenosquamous carcinoma, choriocarcinoma, or even high-grade sarcomas. Colloid carcinomas are extremely rare in MCN, but they occur commonly in IPMN. The molecular pathway of the pathogenesis of MCNs is not clearly understood. K-ras and p53 mutations have been implicated, as well as loss of DPC4. Interestingly, a recent study using a mouse model showed that APC haploinsufficiency coupled with p53 loss resulted in the development of MCN with invasive carcinoma with 100% penetrance.

**Clinical Presentation**

In light of the mandatory presence of the underlying ovarian-type stroma, not surprisingly MCNs are now diagnosed almost entirely in women. This requirement, combined with the usual lack of communication with the pancreatic duct, defines a unique phenotype separate from IPMN. In a combined report from the University of Verona and the Massachusetts General Hospital, Crippa and colleagues reviewed their experience with 163 MCNs that met the WHO criteria for diagnosis. Of the 163 patients, 95% (155 patients) were perimenopausal females. Only eight males were identified, and they were significantly older than the female patients (63 vs 44 years, \( p = .011 \)). The location of MCN within the gland was almost entirely confined to the body and tail of the pancreas (97%), and only five lesions were found in the pancreatic head. In reviewing the literature regarding MCN, these researchers noted the importance of segregating studies according to whether or not the presence of ovarian-type stroma was required for inclusion of pathological specimens within collected reports. Goh et al. reviewed those studies where the presence of ovarian-type stroma was a mandatory criterion for the diagnosis of MCN and found that 99.7% of
the patients were women, the mean age at presentation was 47 (range, 18-95) years, and 95% of MCNs occurred to the left of the pancreatic neck. By comparison, when this criterion was previously not a prerequisite to diagnose MCN, patients were older, more often male, and the lesions were located in the head with a frequency exceeding 30%.

Abdominal pain or discomfort is the most common presenting symptom, occurring in over 70% of patients. A history of acute pancreatitis may also be elicited in 9% to 13% of patients, although less commonly than in patients with IPMN. Patients with an MCN with an associated invasive carcinoma present 11 years later than those with noninvasive neoplasms, likely representing the longer time required to progress to overt malignancy within these neoplasms.

**Diagnosis**

In a female patient with a macrocystic lesion in the body or tail of the pancreas, MCN should be strongly considered. In addition, MCNs have some characteristic features that may be evident during imaging or preoperative evaluation. Classically, MCNs contain large septated cysts with thick irregular walls that may be well visualized on CT, MRI, or ultrasound evaluation. Papillary projections from the epithelium often extend into the cystic cavities and may be visible, particularly on high-quality axial or endoscopic ultrasound imaging. In a minority of cases, the wall of the MCN may contain calcifications, a characteristic associated with a higher likelihood of malignancy. MCNs may also present as large unilocular cysts that may appear similar on cross-sectional imaging to long-standing pseudocysts. Two distinguishing characteristics in this scenario that suggest the diagnosis of MCN are the lack of surrounding inflammatory changes beyond the wall of the neoplasm in MCNs and the absence of pancreatitis. Demonstration of ductal communication with the cyst by MRI or magnetic resonance cholangiopancreatography (MRCP) may distinguish pseudocysts or IPMNs from MCNs, although MCNs can in rare instances exhibit a connection with the pancreatic duct.
Abdominal CT performed on a 69-year-old healthy man who had a palpable abdominal mass detected on routine physical examination. The mass (arrow) was homogeneous in character and was initially presumed to be a pseudocyst. Pylorus-preserving pancreaticoduodenectomy was performed, revealing an 8.5-cm mucinous cystic neoplasm without malignancy.

Similar to SCN, determination of a treatment plan for MCN is predicated upon whether or not a given lesion is mucinous. Analysis of cyst fluid aspirated from MCNs typically show elevated levels of CEA and low amylase concentrations (as MCNs do not typically communicate with the pancreatic ductal system). The Cooperative Pancreatic Cyst Study demonstrated that a cyst fluid CEA value greater than 192 ng/mL achieved the greatest efficiency for differentiating mucinous from nonmucinous lesions. The accuracy of cyst fluid CEA (88/111, 79%) was greater than the accuracy of EUS morphology or cytology (p < .05). No combination of tests further improved diagnostic accuracy. A cyst fluid CEA level greater than 800 ng/mL has a specificity of 98% for predicting MCN, but a sensitivity of only 48%. Khalid and his coinvestigators tested the utility of DNA analysis
of cyst fluid to diagnose mucinous and malignant cysts. The presence of a K-ras mutation was highly specific for a mucinous cyst (96%) but had a low sensitivity of only 45%. A considerable selection bias was introduced by the study design, which may have overestimated the ability of DNA analysis to define a mucinous cyst. Presence of a K-ras mutation in cyst fluid may provide additional information when CEA levels are not discriminative, particularly in lesions that appear to not have clear imaging patterns that allow separation of SCN versus MCN.

A recent multi-institutional review of resected pancreatic cystic neoplasms showed promising results using a combination of a panel of molecular markers known to be implicated in pancreatic cysts and clinical features to predict lesions requiring resection versus observation. In reviewing MCNs, the authors approached 90% sensitivity and 97% specificity with the combination of certain molecular markers (including the absence of CTNNB1 and GNAS mutations, loss of heterozygosity on chromosome 3, and aneuploidy in chromosome 1q and 22q) and the following clinical markers: age <75 years old and the absence of all three of the following features: male sex, communication with the main pancreatic ductal system, and multiple cysts. In addition, as stated in the SCN section, additional biomarkers are being investigated to distinguish between mucinous and nonmucinous cysts.

**Treatment**

In their pooled review of the literature, including 10 studies of MCN defined by ovarian-type stroma, Goh and coworkers noted that in the 40 invasive carcinomas found in 344 patients, only one of the malignant MCNs was less than 4.5 cm in size at the time of resection. Crippa and colleagues noted that lesions containing either in situ or invasive carcinoma were larger (median size 80 vs 45 mm, \( p = .0001 \)), and intracystic nodules or papillae were more frequently present (64% vs 4%, \( p = .0001 \)), when compared with benign neoplasms. All lesions demonstrating cancer on pathology were either greater than 4 cm in diameter or contained nodules by preoperative imaging. Careful observation of asymptomatic lesions less than 3 cm in size, without the presence of nodules, appears to be a reasonable approach for MCN (see Table 72-2). However, a post-hoc analysis by Sawhney and
associates has questioned whether size alone, based on the original Sendai Consensus criteria, is a sufficient predictor of malignancy in pancreatic cysts. Their data indicated that the original consensus guidelines should be applied with caution, and that more accurate diagnoses might be generated by the combination of cyst size and main pancreatic duct dilation greater than 3 mm. Crippa et al. reported a 73% rate of adenoma in their series of resected MCNs; however, this leaves approximately 27% of cases with at least borderline MCN pathology.

Biopsy of MCN should not be utilized to determine the presence of carcinoma, because the presence of invasion within a lesion may be patchy or discontiguous and a negative biopsy result may be obtained erroneously based on sampling error. Due to the significant rate of malignancy and the risk of progression to malignancy associated with MCN, symptomatic neoplasms, lesions greater than 3 cm, or those containing nodules or papillae should undergo resection. In addition, young, fit patients with MCNs should be considered for resection, as the cumulative risk of malignant transformation exceeds life expectancy. As with SCN, enucleation has been documented to be an effective strategy for resection in selected MCN cases. However, there is some risk of performing an inadequate oncologic resection for an MCN should it harbor an invasive component, while there is virtually no risk for SCN. Therefore, enucleation should only be applied to highly selected cases of small, peripherally located MCNs with confirmation of a noninvasive component by extensive frozen-section analysis. Likewise, segmental pancreatic resections for lesions in the pancreatic neck and body (central pancreatectomy) or tail (spleen-preserving distal pancreatectomy) should be performed cautiously in selected patients without any indication of invasive disease. Larger tumors in older patients (ie, patients fitting the characteristics of MCN with an associated invasive cancer) should be treated with formal pancreatic resection to include specimen-associated lymph node harvest. Lesions in the pancreatic head are best treated with pancreaticoduodenectomy, while left-sided lesions are treated via distal pancreatectomy with or without en bloc splenectomy. Extended lymphadenectomy, which has not been shown to definitively improve locoregional control or survival in patients with pancreatic ductal adenocarcinoma, has no role in the treatment of patients with cystic neoplasms. Minimally invasive resection techniques should be considered when appropriate at institutions with considerable experience and
acceptable quality outcomes.

The 5-year disease-specific survival for benign or noninvasive MCN is 100%, but falls to 50% to 60% for patients with invasive mucinous cystadenocarcinoma\textsuperscript{72} (Fig. 72-6). Failure to completely resect a noninvasive MCN may result in a later recurrence (persistence), and a missed opportunity for cure.

![Kaplan–Meier disease-specific actuarial survival curves for invasive MCN (hatched line) and noninvasive MCN (black line) among 163 patients resected at the University of Verona and the Massachusetts General Hospital from 1988 to 2005. Five-year survival for patients with invasive MCN is approximately 57%, while for those with noninvasive MCN it is 100%. (Reproduced with permission from Crippa S, Salvia R, Warshaw AL, et al: Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients, \textit{Ann Surg} 2008 Apr;247(4):571-579.)](image)

Adjuvant chemotherapy or chemoradiation therapy for mucinous cystadenocarcinoma has been poorly investigated and has no proven benefit. A single case report describes the use of neoadjuvant chemoradiation and treatment monitoring by serum CEA level, but no prospective clinical trials have been performed.\textsuperscript{83} Some high-volume centers would likely offer
adjuvant chemotherapy to patients with invasive cystadenocarcinoma, extrapolating from the experience with ductal adenocarcinoma. There are no data to support the utility of adjuvant radiotherapy. Follow-up with serial MR imaging every 6 months for 2 years and annually thereafter appears reasonable for patients with resected MCN with an associated invasive cancer. Patients with resected noninvasive MCNs should receive no postoperative adjuvant therapy and are not typically followed with serial imaging (as they are universally considered cured, with no additional risk for distant recurrence or the remnant gland developing pancreatic cancer).

**INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS**

IPMNs are mucin-producing epithelial tumors arising from the pancreatic ductal system that cause dilation of this system (Table 72-2). The study of IPMN is one of the most rapidly evolving fields in pancreatology, as these are relatively “newly” described pancreatic lesions that in the past were variably referred to as mucinous ductal ectasia, intraductal papillomatosis, intraductal adenoma or adenomatosis, intraductal mucin-secreting tumor, and intraductal papillary mucinous tumor. The earliest report of this “new” lesion is attributed to Ohashi and Maruyama and was published in the Japanese literature in 1982. This report described four malignant lesions associated with the main pancreatic duct and characterized the now well-described copious amounts of mucus that distend and emanate from the ductal system. The authors noted the comparatively better survival of these patients compared to those with classic invasive ductal adenocarcinoma of the pancreas. While many subsequent authors have helped to further characterize the subtleties of IPMN, these initial observations accurately depict typical cases.

In 1996, the WHO first formally recognized IPMN as a distinct entity; establishing criteria for the pathological diagnosis of these lesions. Characteristic features include a tall, columnar epithelium with marked mucin production, and cystic transformation of either the main pancreatic duct or one of its side branches (Fig. 72-7). More recent versions of these diagnostic criteria have allowed the stratification of noninvasive IPMNs based on their degree of dysplastic change and identification of distinct morphologic
FIGURE 72-7  MRCP reconstruction of abdominal MRI of a 73-year-old man who presented with abdominal pain and pancreatitis. The patient underwent a pylorus-preserving pancreaticoduodenectomy; final pathology revealed a main-duct IPMN with moderate-grade dysplasia located in the head of the pancreas. All resection margins were negative for neoplasia. Notable findings on this image characteristic of IPMN include the multiloculated cystic mass in the right side of the pancreas (circle) associated with moderate pancreatic ductal dilatation (arrow).

Improvements in the diagnosis, identification, and stratification of these intraductal lesions offer clinicians the opportunity to safely observe lesions with a very low risk to progress to carcinoma and the ability to intervene surgically when the risk of preinvasive neoplasia is high (or overt invasive
carcinoma exists). At both ends of the spectrum of IPMNs, the management is well substantiated. However, it is the indeterminate lesions where clinical subtleties mean the difference between unnecessary surgical intervention and the “missed” progression to invasive carcinoma. Multiple guideline statements of been developed to assist clinicians, although to this point, none are 100% specific and sensitive (Table 72-3).\textsuperscript{16,17,86} These guidelines are named after the sites of the consensus meetings in Japan—Fukuoka and Sendai.

\begin{table}
\centering
\caption{Comparison and Evaluation of International Consensus Guidelines}
\label{tab:72-3}
\begin{tabular}{|c|c|}
\hline
\textbf{Guideline} & \textbf{Recurrence Rate} \\
\hline
Fukuoka & 0.01 \\
Sendai & 0.05 \\
\hline
\end{tabular}
\end{table}
<table>
<thead>
<tr>
<th>Fukuoka, 2012</th>
<th>Sendai, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend resection (in surgically fit patients)</td>
<td>IPMN</td>
</tr>
<tr>
<td>Obstructive jaundice with cystic lesion in head of pancreas</td>
<td>Obstructive jaundice with cystic lesion in head of pancreas</td>
</tr>
<tr>
<td>Enhancing solid component within cyst</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Main pancreatic duct &gt;10 mm</td>
<td>&gt;3 cm in size</td>
</tr>
<tr>
<td>MCN</td>
<td>1-3 cm with any high-risk stigmata</td>
</tr>
<tr>
<td>All MCN</td>
<td>(ie, mural nodules, dilated main duct, positive cytology)</td>
</tr>
<tr>
<td>If MCN &lt;4 cm without mural nodules, gland sparing resection should be considered</td>
<td></td>
</tr>
<tr>
<td>Recommend further workup (EUS, fluid evaluation, etc.)</td>
<td>IPMN</td>
</tr>
<tr>
<td>History of pancreatitis</td>
<td>History of pancreatitis</td>
</tr>
<tr>
<td>Cyst &gt;3 cm</td>
<td>Cyst &gt;3 cm</td>
</tr>
<tr>
<td>Thickened / enhancing cyst wall</td>
<td>Thickened / enhancing cyst wall</td>
</tr>
<tr>
<td>Main duct size 5-9 mm</td>
<td>Main duct size 5-9 mm</td>
</tr>
<tr>
<td>Nonenhancing mural nodule</td>
<td>Nonenhancing mural nodule</td>
</tr>
<tr>
<td>Abrupt change in pancreatic duct with distal pancreatic atrophy</td>
<td>Abrupt change in pancreatic duct with distal pancreatic atrophy</td>
</tr>
<tr>
<td>Surveillance (in nonresected patients)</td>
<td>IPMN</td>
</tr>
<tr>
<td>&gt;3 cm MRI/EUS q 3-6 months, strongly consider surgery</td>
<td>&gt;3 cm, resection</td>
</tr>
<tr>
<td>2-3 cm MRI/EUS q 3-6 months, consider surgery if long-follow, life 1-2 cm CT/MRI yearly × 2 years, then lengthen &lt;1 cm CT/MRI in 2-3 years</td>
<td>2-3 cm, q 3- to 6-month MRI/CT</td>
</tr>
<tr>
<td>2-3 cm MRI/EUS q 3-6 months, consider surgery if long-follow, life 1-2 cm CT/MRI yearly × 2 years, then lengthen &lt;1 cm CT/MRI in 2-3 years</td>
<td>1-2 cm, q 6- to 12-month MRI/CT</td>
</tr>
<tr>
<td></td>
<td>&lt;1 cm, q 12-month MRI/CT</td>
</tr>
</tbody>
</table>
Pathological Features

Histologically, IPMNs are characterized by intraductal proliferation of mucinous cells which form papillae. Secretion of mucin leads to dilatation of the pancreatic ducts (Fig. 72-8). Lesions may be localized, multicentric, or involve the entire ductal system. The proliferation of mucinous cells may involve the main pancreatic duct (“main duct type,” MD-IPMN), or be confined to the branch ducts (“branch duct type,” BD-IPMN), or show a pattern spanning both areas in a “mixed-type.” The mucosa of IPMNs display the typical range of dysplasia-to-invasive carcinoma sequence. The degree of dysplasia will be classified as either low-, moderate-, or high-grade based on the highest grade present within a resected specimen.

FIGURE 72-8 Gross photograph of a distal pancreatectomy specimen from a patient with an IPMN with carcinoma in situ. Characteristic features include the mass in direct communication with a markedly dilated main pancreatic duct.

IPMNs demonstrate a progressive precursor model of carcinogenesis similar to that seen in colon cancer. Tall mucin-producing columnar epithelial cells that remain well differentiated characterize IPMN adenoma (low-grade dysplasia). Little or no dysplasia is present in these lesions. IPMN
borderline lesions (moderate-grade dysplasia) are described as lesions with moderate epithelial dysplasia, characterized by moderate loss of polarity, changes in nuclear morphology, and pseudopapillary formation (Fig. 72-9). IPMNs with high-grade dysplasia have severe dysplastic changes. These lesions may be papillary or micropapillary. Severely dysplastic lesions may lose the ability to secrete mucin. IPMNs are pathologically similar to pancreatic intraepithelial neoplasia (PanIN) with the caveat that the former are macroscopic lesions while the latter are microscopic. IPMNs, like PanIN lesions, are intraductal lesions that may demonstrate a range of cellular atypia and malignant transformation. However, IPMNs may be distinguished based on their gross visibility and involvement of large ducts. PanINs should be considered a microscopic finding involving ducts less than 5 mm in diameter, while IPMNs are macroscopic findings.90

FIGURE 72-9 Photomicrograph of an IPMN with borderline features. Characteristic features include the tall columnar cells lining the papillary projections of the tumor, moderate dysplastic changes of the epithelium, and varied nuclear morphology.

Further investigation has identified histologic subtypes of the papillae that seem to influence biologic behavior (and ultimately clinical prognosis).
Currently, four morphologic patterns of IPMN can be seen, and include gastric foveolar-type, intestinal-type, pancreatobiliary-type, and intraductal oncocytic papillary-type. In the gastric foveolar-type, mostly seen in BD-IPMNs, the lesion resembles gastric epithelium and demonstrates papillae lined by tall columnar cells with basally oriented nuclei and abundant pale mucin. This pattern is also prevalent in the nonpapillary areas of MD-IPMN. The neoplastic cells in gastric foveolar-type do not express MUC1 and MUC2, but highly express gastric-type mucins including MUC5AC and MUC6, supporting their gastric differentiation. These lesions are generally low-grade (although occasional high-grade lesions can be encountered). Most MD-IPMNs are of the intestinal type and closely resemble colonic villous adenomas, being composed of well-formed, long, finger-like projections lined by columnar mucin-producing neoplastic cells with enlarged nuclei. Typically, moderate-grade or high-grade dysplasia is present. The neoplastic cells of intestinal-type IPMNs do not express MUC1 but strongly express MUC5AC and MUC2. In addition, intestinal-type IPMNs are strongly immunoreactive with antibodies to CDX2. Cancers arising in these IPMNs are typically colloid carcinomas and may have a more favorable prognosis (Fig. 72-10). Pancreatobiliary-type IPMN consists of cuboidal neoplastic cells that are atypical, tend to contain less mucin, and are more frequently high-grade. The immunohistochemical pattern of pancreatobiliary-type IPMNs is similar to that of PanINs, expressing MUC1 and MUC5AC. Invasive cancers associated with the pancreatobiliary morphology are usually tubular, with a histologic structure similar to typical ductal adenocarcinoma. The more recently defined fourth histologic subtype of IPMN is intraductal oncocytic papillary neoplasms. These lesions are very rare, with a complex architecture with arborizing papillae, cribriform formations, and solid nests, all growing into the lumina of the dilated duct. They demonstrate a characteristic abundant eosinophilic cytoplasm due to accumulation of mitochondria, and express MUC1 and MUC6. Typically high-grade lesions, invasive carcinoma arising from these oncocytic lesions may retain the oncocytic cytology. Interestingly, they tend to lack the KRAS mutation seen in typical ductal adenocarcinoma and seem to exhibit excellent long-term prognosis and survival. While both the villous-intestinal and the pancreatobiliary types may be found alongside the gastric-foveolar type, it is uncommon to identify both the villous-intestinal and pancreatobiliary type of
papillae in the same IPMN. Differentiation of histologic subtypes may help predict the prognosis of IPMNs. Invasive carcinomas developing in a background of intestinal subtypes typically are colloid carcinomas and have a generally more favorable 5-year survival (70%-83%) compared with tubular ductal carcinoma arising in the background of pancreatobiliary IPMN (24%-50% 5-year survival). In addition, a recent review of the rare oncocytic-type had a 46% recurrence rate after 10 years; however, no patients died of the disease at median follow-up of 7 years.

FIGURE 72-10 Photomicrograph of a colloid carcinoma within an IPMN. Note the largely acellular nature of these cancers and their abundant mucus production.

IPMNs appear also to have distinct molecular events contributing to the clinical and pathological behavior that further distinguish them from lesions in the PanIN–ductal adenocarcinoma sequence. Iacobuzio-Donahue and associates described the intact (normal) expression of the tumor-suppressor gene \( Dpc4 \) in the intraductal components of 79 IPMNs. In contrast, \( Dpc4 \) inactivation has been shown to be relatively specific for pancreatic adenocarcinoma, and its persistence in both noninvasive and invasive IPMNs
argues that these lesions may arise through a pathway that is distinct from the PanIN–ductal adenocarcinoma sequence. IPMNs also appear to have a significantly lower rate of KRAS and p53 mutations, which are common in ductal adenocarcinoma. Fritz and coworkers demonstrated that losses of chromosome 5q, 6q, and 11q were significantly higher in IPMNs with high-grade dysplasia or invasion compared with classic ductal adenocarcinoma. These data and others suggest that IPMNs are unique pancreatic neoplasms, with a pathogenesis that is distinct from that of the PanIN–ductal adenocarcinoma sequence. In addition, while many of the common genetic mutations seen in standard ductal adenocarcinoma are present in IPMN, they tend to occur much less frequently. Also, other mutations have been discovered that occur in some IPMNs (such as PIK3CA and GNAS) and not in standard pancreatic ductal adenocarcinoma. Recently, Tan and colleagues showed that mutations in KRAS and GNAS do occur early in IPMN carcinogenesis, with mutations in GNAS predominant in colloid carcinoma, and KRAS mutations predominant in tubular carcinoma. In addition, these mutations showed some ability to predict outcome in IPMN-associated invasive carcinoma, with GNAS mutated colloid carcinoma showing excellent survival at 4 years post-resection.

Clinical Presentation

The biologic behavior of IPMNs parallels their classification according to their distribution within the pancreatic ductal system. Main duct type and combined main duct and branch duct type lesions (mixed-type) are more likely to present with symptoms, while strictly BD-IPMNs are more frequently detected as asymptomatic cystic neoplasms on cross-sectional imaging. Pancreatitis is seen more commonly in MD-IPMN, possibly related to mucin plugging the main duct and the ampulla. In a combined experience of the Massachusetts General Hospital and the University of Verona reported by Salvia and colleagues, acute pancreatitis occurred in 23% of 140 patients with main duct variant IPMN. A recent review, again by the group at the Massachusetts General Hospital, identified that 21% of patients who underwent resection for IPMN presented with at least one episode of acute pancreatitis. In this setting, an episode of pancreatitis was associated with intestinal subtype, malignancy, and main duct
Both genders are affected by IPMNs, with a moderate male predominance in some series. Patients with IPMN tend to be older, with a mean age of 65 years, as compared with those having MCN, who are predominantly perimenopausal. Patients diagnosed with invasive MD-IPMNs are typically 5 or more years older than those patients with noninvasive MD-IPMNs. This interesting observation again supports the adenoma-carcinoma sequence theory and gives some insight into the amount of time required for progression along this sequence. Malignant IPMNs are more likely to present with symptoms typically attributed to ductal adenocarcinoma, such as obstructive jaundice and weight loss.

The development of symptoms more commonly attributed to ductal adenocarcinoma in patients with IPMN may herald the occurrence of carcinoma either synchronously or metachronously in the gland. Several studies have demonstrated the presence of an invasive ductal adenocarcinoma elsewhere in the pancreas, distinct from the location of the cystic neoplasm in up to 10% of IPMN patients. Ingkakul and colleagues showed that in a multivariate analysis, worsening diabetes (odds ratio 15.73 [95% CI: 4.40-56.25]; p < .001), and an abnormal serum CA 19-9 (odds ratio 3.70 [95% CI: 1.19-11.48]; p = .024) are independent factors predictive of synchronous or metachronous separate ductal adenocarcinoma in patients with IPMN. A recent review of 223 patients with IPMNs with main duct involvement showed that 43% of patients presented without symptoms, while the most common presenting symptoms were weight loss (32%), pancreatitis (26%), and obstructive jaundice (14%). In addition, the incidence of extrapancreatic malignancies appears to be higher in patients with IPMN. The development of colorectal adenomas and carcinomas, Barrett mucosa, and gastric carcinomas appear to be important accompanying entities seen in IPMN patients.

**Diagnosis**

Distinguishing IPMNs from other cystic pancreatic neoplasia can at times be challenging. The International Association of Pancreatology consensus guidelines of 2012 (Fukuoka) summarize the evaluation and treatment for mucinous cystic lesions of the pancreas (IPMN and MCN) with the best
supporting evidence available at the time (Table 72-3).\textsuperscript{16,17} Despite these guidelines (which are revised from the initial “Sendai” guidelines of 2006), clinicians will still have difficulty at times accurately selecting patients in which true preinvasive (or invasive) neoplasia is present (and thus require operative intervention). When evaluating IPMNs, it is important to classify the lesion as either having evidence of invasive cancer, high-risk stigmata, or strictly benign characteristics. Typically this is accomplished with a combination of imaging modalities. High-quality multidetector CT imaging (with thin sections through the pancreas) is primarily used in the evaluation of pancreatic and associated lesions. This modality provides excellent visualization and classification of pancreatic cystic neoplasia, as well as the surrounding pancreatic parenchyma (which may be a site of an adjacent malignancy). In addition, high-quality CT imaging can identify septations, mural nodules, and calcifications within the cystic lesions. While advancements in CT imaging abound, abdominal MRI imaging, particularly in combination with MRCP reconstruction, remains a reliable and equally efficacious tool in the identification of IPMNs. Importantly, MRI/MRCP can often accurately identify whether there is communication with the pancreatic ductal system and the cystic lesion. This may help distinguish between small branch duct IPMNs and other cystic lesions. IPMNs characteristically appear as cystic masses resulting from dilatation of the main pancreatic duct or side branch ducts. Polypoid projections (mural nodules) into the cystic spaces may be present. Approximately half of IPMNs occur in the pancreatic head, although they may be present anywhere within the pancreas and can diffusely involve the entire gland. Currently, MRCP is the modality of choice for defining mural nodules, demonstration of the communication of the cystic neoplasm with the pancreatic ductal system, and evaluating the extent of the pancreatic ductal dilatation.\textsuperscript{107} Use of MRCP has largely supplanted endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of IPMN, since MRCP is noninvasive, does not require sedation, and does not carry the risks of pancreatitis and perforation that accompany ERCP.

In order to appropriately classify IPMNs (observation vs resection), a thorough search for “high-risk” characteristics is necessary. The 2012 Fukuoka consensus guidelines list the following as high-risk stigmata (requiring operative intervention in appropriate patients): obstructive jaundice in the setting of a cystic mass in the head of pancreas, an enhancing solid component within a cyst, or main pancreatic duct dilation $>10$ mm. In
addition, “worrisome” characteristics (requiring additional workup with EUS) are defined as the following: a cyst ≥3 cm, thickened or enhancing cystic wall, main pancreatic duct size 5 to 9 mm, nonenhancing mural nodule, or abrupt change in caliber of pancreatic duct with distal pancreatic gland atrophy. In combination with clinical history, this guideline frames an algorithm for clinicians to stratify patients.

The initial Sendai consensus guidelines published in 2006 included a cyst >3 cm in size in the “high-risk” group. This was based on available data at the time that revealed imaging features suggestive of the presence of malignancy, including tumor size (cyst diameter ≥30, 40, or 50 mm), MD-IPMN, main duct dilatation greater than or equal to 10 or 15 mm, patulous papilla, mural nodules (≥ 3, 5, or 10 mm in size), presence of biliary ductal dilatation greater than or equal to 15 mm, a solid mass, or occurrence of an area of abnormal attenuation in the surrounding pancreas. Importantly, Salvia and colleagues, in Verona, Italy, followed 121 patients with multifocal branch duct IPMN (median diameter of the largest lesion being 1.7 cm) over a 40-month observation period. All of the 121 patients remained alive, without surgery, and all remained asymptomatic. Thus, there is clearly a role for conservatism in the management of patients with BD-IPMNs and no additional worrisome features. Critical review of these initial Sendai guidelines confirmed the rising practice leading to resection of low-grade BD-IPMNs utilizing the >3 cm size criteria. This ultimately prompted the “revised” Fukuoka consensus guidelines published in 2012 to change the >3 cm size criteria to a “worrisome” feature instead of a “high-risk” feature (See Table 72-3), perhaps favoring a more conservative posture.

Recently, Ammori and colleagues reviewed their experience with resected IPMNs, specifically examining cases with either isolated uncinate process ductal dilation or a combination of main pancreatic duct and uncinate process ductal dilation. In 184 cases, 47 patients had dilation of the uncinate process duct and 50 patients had an uncinate process cystic lesion. While uncinate process cystic lesions were not associated with high-grade dysplasia or invasive carcinoma (pathologic IPMN), dilation of the uncinate process duct was associated with pathologic IPMN in 64% of cases. In cases of only uncinate process duct dilation (without associated main pancreatic duct dilation), 65% of patients harbored high-grade dysplasia or invasive carcinoma. This is in stark contrast to the 18% of patients who harbored pathologic IPMN in the setting of only branch-duct dilation (without main
pancreatic or uncinate duct dilation). These data suggest that uncinate process duct dilation may be considered an additional risk factor for pathologic IPMN.\textsuperscript{117}

EUS is an important adjunct in select patients requiring further investigation (worrisome features). Ohno et al. demonstrated that the finding of a papillary mural nodule or a nodule exhibiting an invasive component on EUS was predictive of malignancy with a sensitivity of 60\%, specificity of 93\%, and an accuracy of 76\%.\textsuperscript{118} EUS-FNA may also be useful in reinforcing a decision not to resect a BD-IPMN if it is otherwise without features predictive of malignancy. Marie and colleagues found that the combination of a CEA level less than 200 ng/mL and a CA 19.9 level greater than 40 U/mL retrieved from the cystic material of an IPMN together had a 96\% negative predictive value for the diagnosis of malignancy.\textsuperscript{119} In addition, endoscopic sampling of cyst fluid is an area of active investigation at many high volume centers. Unfortunately, results have been less than definitive. Cyst fluid CEA and amylase may add important objective data, however, is not universally consistent. Interestingly, cytologic or molecular analysis (such as cyst inflammatory markers) may allow for advancements in diagnosis, and continues to be an area of active investigation.\textsuperscript{120}

The addition of positron emission tomography (PET) with CT (PET/CT) using 18F-fluoro-deoxyglucose has been investigated in an effort to improve identification of IPMN with high-grade dysplasia or invasive carcinoma. Recently, Roch et al. studied the use of PET/CT in combination with the 2012 International Consensus Guidelines and found an increase of the sensitivity and specificity of detecting IPMN with malignancy to 78\% and 100\%, respectively. In addition, the combination of PET/CT and guideline criteria increased the sensitivity and specificity in detecting IPMN with high-grade dysplasia to 100\% and 71\%, respectively.\textsuperscript{121}

With the creation of the Sendai and Fukuoka guidelines, as well guidelines from the American Gastroenterological Association,\textsuperscript{16,17,86} debate on the appropriate management of pancreatic cystic neoplasia continues. Fundamental differences in the viewpoint regarding the risks of pancreatic surgery and the risk of progression to malignancy allows for discord between clinicians managing patients affected with pancreatic cysts. In addition, the relatively new nature of this field of study lends for confusing, at times conflicting, and typically low-quality data, making definitive management
guidelines challenging. Thus, clinicians managing these patients must take into account the individual patient situation as well as all available information on the cyst (ie, imaging characteristics, etc), as well as access to high-volume quality pancreatic surgeons. Critical appraisal of the updated Fukuoka guidelines both confirms and questions the accuracy of strict adherence in detecting malignant cysts. Kaimakliotis and colleagues compared the original Sendai criteria to the updated Fukuoka guidelines and showed no difference in either guideline in predicting patients with advanced neoplasia; however, two patients considered “low risk” using the Fukuoka guidelines had high-grade dysplasia. Recent reviews, including a systemic review of 1382 patients, confirm that some malignant IPMNs would be missed with strict adherence to the Fukuoka guidelines. These reviews underscore the imprecise nature of the best expert consensus guidelines and the need for patient-specific consideration on a case-by-case basis (with the inclusion of pancreatic surgeons).

**Treatment**

The goals of treatment for IPMN include minimizing the exposure to unnecessary surgical risk while optimizing the removal of all premalignant neoplasia and frank carcinoma. In addition, the natural history of IPMN must be compared to the individual patient’s clinical status and situation. The Japan Pancreas Society performed a multi-institutional, retrospective study of 1379 cases of IPMN drawn from 98 of their member programs in 2004. The clinicopathologic features of benign IPMN (adenoma [low-grade dysplasia] and borderline lesions [moderate dysplasia]; n = 564) were strikingly different when compared with tumors containing frank adenocarcinoma (n = 445). Patients with adenocarcinoma were significantly older (67 vs 65 years, p = .0002) and more frequently symptomatic (49 vs 35%, p < .0001), as compared to the noncarcinoma group. Cancer occurred more commonly in either main duct-type or combined-type tumors, as compared to branch duct-type neoplasms (60%, 65%, and 30% respectively, p < .001). The preoperative imaging of patients who were subsequently found to have adenocarcinoma on pathology demonstrated a higher incidence (63% vs 28%) and size of mural nodules (12 vs 5 mm) when compared with those who had benign lesions (both p < .0001). Branch duct-type tumors with
cancer were larger (35 vs 28 mm, \( p < .0001 \)) than those without cancer.

Based on the data generated in the earlier report, the International Association of Pancreatology convened a consensus conference in Sendai, Japan, in 2004. The subsequent guidelines published in 2006 (and then revised in 2012) have become a new benchmark for the management of IPMN (Table 72-3).\(^{16,17}\) The current “Fukuoka” guidelines recommend the resection of all IPMN of a main duct type and mixed variants, those showing main pancreatic duct dilatation greater than or equal to 10 mm, as well as those with the presence of enhancing mural nodules (solid components), or a positive cytology, provided the patients are reasonable candidates for surgery with an acceptable life expectancy. All symptomatic IPMNs (abdominal pain or obstructive jaundice) were deemed to warrant resection. These recommendations were predicated upon the risk of carcinoma in symptomatic or main duct type lesions. Additional “worrisome” stigmata were included in the guidelines, and patients with these stigmata should undergo additional work-up with endoscopic ultrasound evaluation. These stigmata include cyst size greater than 3 cm, prior pancreatitis, thickened or enhancing cyst wall, main pancreatic duct size of 5 to 9 mm, nonenhancing mural nodule, or an abrupt change in the caliber of the main pancreatic duct with distal gland atrophy. And while the original “Sendai” guidelines recommended that BD-IPMNs greater than 30 mm in diameter undergo resection, more recent data suggest that this may overtreat many patients with low-grade pathology. This has led to the revision of the guidelines to move BD-IPMN greater than 3 cm to the “worrisome” group requiring further investigation, instead of recommending surgical resection for these cysts without further worrisome features. Data suggest that BD-IPMNs less than 30 mm in diameter, without evidence of mural nodules or main duct dilatation, have low malignant potential and that such patients are candidates for careful observation. At follow-up examinations, appearance of symptoms, cyst enlargement to greater than 30 mm, detection of positive cytology on FNA, development or identification of mural nodules or main pancreatic duct dilatation (≥6 mm) were deemed indications for resection.

Since the development and revision of the Sendai guidelines, much of the subsequent literature has sought to examine the accuracy of the recommendations, particularly with regard to the observation of asymptomatic BD-IPMN. Pelaez-Luna and colleagues identified 147 patients with BD-IPMN, of whom 66 underwent resection at diagnosis and 81 were
followed over time (of which 11 were resected during the follow-up period). Of the patients undergoing resection who demonstrated Sendai consensus guideline indications for surgical therapy, 9/61 (15%) had carcinoma on pathology, whereas none of the 16 patients without consensus indications for resection had malignancy ($p = .1$). A single guideline indication for resection taken as an indicator of carcinoma had a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 23%, 14%, and 100%, respectively.

Several studies have suggested that the development of mural nodules is predictive of the risk of developing malignancy, while a progressive dilatation of duct size remains controversial. Schmidt and colleagues identified 103 patients with BD-IPMN. The mean size of the 20 malignant lesions was $2.0 \pm 0.1$ cm, while the mean size of the nonmalignant neoplasms was $2.2 \pm 0.1$ cm, suggesting that size alone is an insufficient indicator of malignancy. In multivariate analysis, only the presence of mural nodules and atypical cytopathology were predictive of the presence of carcinoma. Tanno et al. prospectively followed 82 patients with flat lesions within BD-IPMN diagnosed by CT or MR and EUS. During a median follow-up of 59 months, 9/82 patients (11%) exhibited progressive dilatation of the cystic lesion. Six elected to continue regular screening, while three underwent resection; the IPMNs resected were staged as IPMN-adenoma in two and IPMN-borderline in one. Four patients (5%) developed mural nodules during a median follow-up of 105 months. All four of these individuals were resected, demonstrating IPMN-adenoma in three and carcinoma in situ in the fourth. Sixty-nine of the 82 patients (84%) showed no changes in their dilated branch duct lesions over a median follow-up of 57 months.

A study from Kyushu University in 2009 attempted to determine whether cyst size is predictive of the malignant potential in flat BD-IPMN. One hundred seventy patients with BD-IPMNs without mural nodules were retrospectively identified from their previous 10-year experience. Seventy-three patients underwent resection of their IPMN: 26 patients had lesions less than 30 mm in size, while 47 patients had neoplasms greater than 30 mm in diameter. Importantly, all of the noninvasive ($n = 5$) and invasive ($n = 1$) malignancies were seen in the IPMN of greater than or equal to 30 mm. In a similar report, Salvia and coworkers followed 89 patients with flat BD-IPMNs less than or equal to 3.5 cm in size for a median time period of 32
months.\textsuperscript{130} Five patients (5.6\%) exhibited an increase in diameter of the cystic lesion, none of which demonstrated carcinoma in the resection specimen pathologically. Alternatively, a study by Fritz and colleagues identified malignancy (invasive carcinoma or high-grade dysplasia) in 25\% of “Sendai Negative” branch-duct IPMNs that were resected at their institution.\textsuperscript{131} Clearly, longer follow-up and further investigation will be needed to determine whether or not these guidelines accurately predict high-risk or malignant disease in small, flat, asymptomatic BD-IPMNs. As might be anticipated, increasing knowledge and follow-up have raised questions about the universal accuracy of the consensus guidelines.

The majority of studies, particularly those following IPMNs conservatively in a prospective fashion, would suggest that the development of invasive carcinoma in flat BD-IPMN less than 30 mm in size is unusual. The occurrence of high-risk stigmata (mural nodules, dilated main duct, or positive cytology) clearly has great predictive value for the ultimate finding of malignancy. EUS appears to be an important adjuvant to fully evaluate IPMN patients for the presence of mural nodules, as well as for aspiration of cytologic specimens. Some authorities insist that any lesion that is to be followed conservatively should be examined by EUS at regular intervals. We have tended to use MRI or MRCP for serial surveillance of small (<3 cm) BD-IPMNs, as this is a noninvasive procedure (as compared to EUS) which avoids radiation exposure (as compared to CT).

Given the excellent survival following resection of IPMNs free of an invasive component, every effort must be made to define lesions at risk for the development of carcinoma at the earliest point possible (Fig. 72-11). Schnelldorfer and coworkers have demonstrated that the survival after pancreatectomy of patients with IPMN with invasive adenocarcinoma is roughly equivalent to that of a matched cohort of patients following resection of ductal adenocarcinoma (median survival, 32 vs 21 months; 5-year survival rate, 31 vs 24\%; \( p = .26 \)).\textsuperscript{132} Other studies have revealed that survival of resected patients without lymph node involvement and invasive IPMN is quite good, while patients with lymph node involvement and invasive IPMN have equivalent outcomes to patients with lymph node–positive pancreatic ductal adenocarcinoma.\textsuperscript{5} A recent study by Marchegiani et al. of 223 resected IPMNs involving the main duct revealed a 69\% 5-year survival, which is significantly better than standard pancreatic ductal adenocarcinoma (Fig. 72-
Winter and colleagues reviewed a multi-institutional experience of resected IPMNs with a small (<20 mm) invasive component and while 5-year survival was 59%, the recurrence rate was as high as 24%, with lymph node metastasis present in 19% of cases (Fig. 72-12). Thus, although overall survival appears to be improved, there is a real risk of recurrence and aggressive disease despite only small foci of invasive carcinoma. Despite the poor survival in patients with invasive disease, surgery remains the best opportunity for cure. Swartz et al. have recently shown that adjuvant chemoradiotherapy confers a 57% decrease in the relative risk of mortality after pancreaticoduodenectomy for invasive IPMN after adjusting for major confounders. This effect was most significant in patients with lymph node metastases or positive surgical margins.

FIGURE 72-11 Kaplan–Meier overall survival curves comparing 106 patients with noninvasive IPMN to 67 patients with invasive IPMN following pancreatic resection at the Massachusetts General Hospital (1990-2013). Patients with noninvasive IPMN have a significantly greater survival than those with invasive carcinoma ($p < .001$). (Reproduced with permission from


**Main Duct IPMN/Mixed-Type IPMN**

Treatment of IPMN depends upon the predicted risk of malignancy or high-grade dysplasia. A distinction between main duct or mixed-type IPMN and branch duct IPMN is important, as generally the risk of high-grade dysplasia or invasive cancer is as high as 60% in main-duct or mixed-type. Thus, once the diagnosis of MD-IPMN is made, resection should be considered in the fit surgical candidate; however, controversy surrounds the extent and type of resection necessary. Generally, the goal of operative intervention is the removal of all high-risk disease and invasive cancer. This typically requires pancreaticoduodenectomy for disease within the head/uncinated process of the pancreas and distal pancreatectomy with en bloc splenectomy for disease located in the body or tail of the pancreas. When operating for highly-suspected (or confirmed) invasive cancer, pancreatectomy should be completed to remove all invasive disease; however, we often avoid total...
pancreatectomy to remove residual noninvasive IPMN at a surgical margin (as distant metastasis becomes a more likely outcome than synchronous invasive cancer within the remnant pancreas). Due to the endocrine liability and other associated morbidity after total pancreatectomy, we recommend using this operation sparingly.

In patients without overt evidence of malignancy and confined disease, segmental pancreatectomy depending on location should be performed. We typically utilize intraoperative frozen section analysis of the pancreatic margin in order to identify any lesion with high-grade dysplasia or occult invasive cancer. If any high-risk disease is identified at the margin, the resection should be extended. In the setting of main or mixed type IPMN with a diffusely dilated pancreatic duct, determining the extent of resection can be challenging. Diffuse pancreatic ductal dilation may be secondary to mucin obstruction of the duct (either proximally or distally to the lesion itself) or may be evidence of disease within the entire duct. When there is an associated intraductal mass, nodule, or obvious cystic lesion, segmental pancreatectomy may be performed. It is our practice at the Thomas Jefferson University Hospital to use intraoperative flexible pancreatoscopy in order to evaluate the residual remnant pancreatic duct for evidence of papillary projections, mural nodules, or other stigmata of IPMN. If any of these findings are present, strong consideration (based on patient characteristics) is given to extend the resection to include the abnormality (Fig. 72-13). In patients with a diffusely dilated pancreatic duct without any associated signs of an intraductal mass/lesion, strong consideration must be given to total pancreatectomy. However, the risk of developing malignancy must be weighed with the morbidity and mortality associated with total pancreatectomy. We typically reserve this option for fit patients who have a long life expectancy (and thus a longer time for progression to invasive cancer in a nonresected state). When residual pancreatic parenchyma remains after resection, surveillance of the gland is required. Surveillance is typically performed by cross-sectional imaging at varying intervals based on degree of dysplasia seen in the resected gland and if any macroscopic abnormalities exist in the remnant gland. If invasive carcinoma is discovered in the resected specimen, surveillance should be performed as for routine pancreatic ductal adenocarcinoma (evaluating for metastatic, recurrent, or synchronous disease).
Camera system is attached to a 7.5 French flexible choledochoscope.

"Pancreatoscope" is inserted into pancreatic duct at site of transection...

and passed as far dista as possible in remnant duct.
Normal dilated pancreatic duct

Dilated pancreatic duct with cobblestoning and nodularity

Dilated pancreatic duct with papillary projections and adherent mucin
Branch Duct IPMN

Based on resectional studies, the risk of malignancy in BD-IPMNs seems to be much less than mixed-type and MD-IPMNs. As such, resection for BD-IPMN should be considered more carefully to assess for evidence of invasive cancer or high-risk stigmata. According to the initial Sendai guidelines, BD-IPMNs greater than 3 cm, those with evidence of mural nodules, or those lesions that cause symptoms should be considered for resection. Since the initial guidelines (and revision), many institutional reviews of resected BD-IPMNs have been published to support and criticize the criteria. While some groups recommend more conservative management than the criteria, other groups have shown a real risk of invasive cancer or high-grade dysplasia in patients with BD-IPMNs for which the guidelines would recommend no surgical treatment.\footnote{131}

An additional consideration unique to the branch-duct type of IPMN (especially small-sized lesions) is distinguishing between IPMN and other small pancreatic cysts (either mucinous or nonmucinous). This distinction is sometimes impossible to identify preoperatively. This necessitates a selective approach to cystic neoplasms of the pancreas in general. Many groups will not perform resection in lesions smaller than 3 cm without worrisome features (solid components, mural nodules, increasing size). In addition, the age and surgical fitness of the patient will play a role in the decision-making in this circumstance. Also, the institutional surgical outcomes for pancreatic resections are important factors to consider and to balance with the risk of malignancy.

Resectional principles for BD-IPMN should be in line with MD-IPMN or mixed-type, with the goal of oncologic resection of all high-grade dysplasia or invasive carcinoma. Surveillance of the remnant pancreas should follow
accordingly, based on the degree of dysplasia (or presence of invasive carcinoma) in the resected specimen. Typically considered a “field defect,” the remaining pancreas is at risk for malignant transformation.

Use of the Fukuoka consensus guidelines means that the preponderance of resections for IPMN will be performed with at least a suspicion of the presence of carcinoma. Targeted pancreatectomies, either pancreaticoduodenectomy or distal pancreatectomy with en bloc splenectomy, have been advocated so as to adhere to oncologic principles of resection. Most centers have advocated the use of frozen-section examination of the pancreatic margin, with attempted clearance of microscopically malignant margins by re-resection and occasional conversion to total pancreatectomy when needed to achieve negative margins. Skip lesions clearly occur, such that a normal resection margin may not be indicative of a lack of neoplasia in the pancreatic remnant. A report by Nara et al. from Tokyo analyzed 130 consecutive patients undergoing resection for IPMN with frozen-section analysis of the pancreatic margin. While the majority of initial frozen-section results showed no neoplasia at the margin, 29 patients had additional pancreas resected for “positive” frozen-section results (12 for low or moderate dysplasia, 10 for high-grade dysplasia, 1 for floating cancer cells, and 6 for invasive cancer). Most patients who recurred following reresection had their recurrence at a distance from the pancreatic margin (peritoneum, liver, and lymph nodes), raising doubt about the true value of reresection for margins determined to be positive at frozen section. The role of total pancreatectomy to achieve clearance of all dysplastic epithelium, even prophylactic total pancreatectomy, is controversial. Notably, of the 84 patients with noninvasive IPMN described by Sohn and colleagues, 7 patients developed recurrent disease in the pancreatic remnant. Negative margins at resection do not eliminate the need for chronic surveillance of the pancreatic remnant, perhaps best done by annual MRI/MRCP.

UNUSUAL PANCREATIC CYSTIC NEOPLASMS

Solid Pseudopapillary Neoplasm (Solid and Papillary Neoplasm)
These rare tumors (approximately 1%-3% of all pancreatic tumors) first described by Frantz in 1959 and then further classified by Hamoudi are notable for several characteristic clinical and pathological features. The ratio of women to men is roughly 10:1, with lesions typically appearing in the second or third decade of life (mean age 22 years, range 2-85 years). Patients often present either with abdominal pain or a palpable abdominal mass. The lesions may be large, presenting in one review at a mean size of 6.1 cm (range 0.5-34.5 cm). On CT, these tumors often appear well circumscribed, with hypodense areas representing hemorrhage or necrosis (Fig. 72-14). Lesions can be evenly distributed throughout the pancreas, although around 70% of tumors arise in the left of the gland. β-catenin mutations are pathognomonic for these tumors, and in addition, most lesions express the beta subtype of estrogen receptors and stain for galectin-3. Although the vast majority of these tumors are benign, some may be considered low-grade malignancies, with local invasion into contiguous structures and occasional distant metastases (roughly 10%-15% of cases). A recent multi-institutional review from Korea reported only 9 out of 317 (2.8%) patients had recurrence after surgical resection. Three clinically detectable parameters were found to be statistically significant to predict recurrence: tumor size >8 cm, microscopic malignant features (cellular pleomorphism, capsule invasion, peripancreatic fat invasion, perineural invasion, lymphovascular invasion, lymph node metastasis), and Stage 4 disease (hepatic or peritoneal metastasis). An aggressive surgical approach is warranted for both the primary and metastatic disease, as 5-year survival in completely resected patients exceeds 95%.
FIGURE 72-14 Abdominal CT scan of a 29-year-old woman with a right-sided solid and papillary neoplasm. A. The tumor (T) resides within the duodenal C loop, and there is some deformation of the portal vein. B. On this more inferior image the tumor (T) is seen to further deform the superior mesenteric vein (SMV), but not touch the superior mesenteric artery. The tumor was resected via a pylorus-preserving pancreaticoduodenectomy, which was extended to include the proximal body of the pancreas. The tumor was dissected free from the SMV and portal vein, and no venous resection was needed.

Cystic Pancreatic Endocrine Neoplasms

Endocrine tumors showing partial or complete cystic components are uncommon. The Cooperative Pancreatic Cyst Study demonstrated only 5 of these lesions out of 341 cystic neoplasms. Immunohistochemical staining of cytological specimens obtained by EUS-FNA demonstrating endocrine markers confirms the diagnosis.\textsuperscript{142,143} In a retrospective review of 170 patients undergoing resection for a pancreatic endocrine tumor at the Massachusetts General Hospital over a 30-year period, 29 cystic endocrine tumors were identified.\textsuperscript{144} Ten (34\%) of the cystic lesions were purely cystic, while 19 (66\%) were partially cystic. Cystic neuroendocrine neoplasms were larger (49 vs 23.5 mm, \(p < .05\)), more likely to be symptomatic (73 vs 45\%, \(p < .05\)), and more likely to be nonfunctional (80 vs 50\%, \(p < .05\)) when compared with solid pancreatic neuroendocrine lesions. The propensity for metastases, invasion, and survival (87 vs 77\% at 5 years, \(p = .38\)) in patients
with cystic lesions was the same as in those with solid pancreatic endocrine neoplasms. More recently, Koh and colleagues performed a systematic review and meta-analysis of solid versus cystic pancreatic endocrine tumors. This review showed that cystic endocrine tumors were more likely to have benign characteristics, be nonfunctional, have a lower mitotic count and Ki67 index, and were less likely to have lymph node metastasis. Interestingly, the 5-year overall and disease-free survivals were similar to solid tumors. Thus, these lesions have a favorable prognosis if completely resected and should be treated aggressively and with similar technique as for a solid endocrine tumor in appropriate surgical candidates, although consideration of nonoperative management is reasonable in high surgical risk patients.

**Cystic Acinar Cell Neoplasms**

Acinar cell carcinoma of the pancreas is a rare neoplasm; however, several recent registry reviews and multi-institutional series have better defined this entity. This lesion has a 2:1 male predominance and although many individuals will present with advanced disease, stage-specific survival is statistically better than that seen in ductal pancreatic adenocarcinoma. Occasionally, acinar cell carcinoma may display an intraductal, papillary, or papillocystic growth pattern and may appear to mimic IPMN with a cystic component. A significant proportion of these tumors (up to 40%) may demonstrate a concomitant endocrine neoplasm. Acinar cell neoplasms with intraductal growth patterns tend to present somewhat earlier than typical acinar cell carcinoma, secondary to the pancreatitis resulting from duct obstruction. Characteristic immunohistochemical staining for trypsin and chymotrypsin as well as the presence of eosinophilic granular cytoplasm in acinar cell carcinoma are helpful in establishing the correct diagnosis. In addition, acinar cell cystadenoma, a very rare benign lesion that lacks mitotic figures (differentiating them from acinar cell carcinoma), has been described, with approximately 20 cases in the literature.

**Cystic Degeneration of Pancreatic Ductal Adenocarcinoma**
While not truly a distinct lesion, it is important to note that pancreatic ductal adenocarcinoma may present with cystic features.\textsuperscript{149} Thus all cystic lesions should at least be considered as potential pancreatic ductal adenocarcinomas until an alternative diagnosis is established. In a comparative review of symptomatic and incidental pancreatic cysts by Fernandez-del Castillo and colleagues, 9\% of symptomatic lesions and 2\% of incidental cysts proved to harbor pancreatic ductal adenocarcinoma.\textsuperscript{55} Adenocarcinomas that obstruct the pancreatic duct may be associated with retention cysts in up to 8\% of patients.\textsuperscript{150}

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INTRODUCTION

Periampullary adenocarcinomas are a set of neoplasms that arise near the ampulla of Vater. Although they are all adenocarcinomas, they arise from the different mucosal tissues of the pancreatic duct, bile duct, ampulla, and duodenum. They are often discussed together because they often share a common clinical presentation, they can be hard to distinguish on cross-sectional imaging, and when respectable, they are treated with pancreaticoduodenectomy.

Pancreatic adenocarcinoma is by far the most common of the 4 periampullary tumors. In fact, in 2016, it became the third most common cause of cancer death in the United States, and it is predicted that in the near future, it will become the second most common cause of cancer death.1 Pancreatic adenocarcinoma accounts for a vast majority of the periampullary
cancers, with the other 3 types being much less frequent. The 4 cancers have different resectability rates and long-term survival rates. Long-term survival is dependent on where cancer arose from, stage at diagnosis, degree of differentiation, and ability to completely resect cancer with negative margins.

In addition to these 4 types of adenocarcinomas, other less common tumors arise in the periampullary region including neuroendocrine tumors, acinar cell cancers, squamous cell carcinomas, gastrointestinal tumors, lymphoma, and metastases from other sites.

PERIAMPULLARY CANCER TYPES

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma is the third leading cause of cancer death in the United States. In 2016, there will be an estimated 53,000 new cases diagnosed with 42,000 deaths from this disease.\(^1\)\(^2\) The peak incidence of pancreatic cancer occurs in the seventh decade of life. African Americans have a higher risk of developing pancreatic ductal adenocarcinoma than do whites. There is a slightly higher incidence in men compared to women. The lifetime risk of developing pancreatic cancer is 1 in 65 and 1 in 67 in men and women, respectively, in the United States. Smoking is one of the strongest risk factors for the development of pancreatic cancer. Obesity has also been implicated, and other factors, such as diabetes and alcohol use, have also been implicated.

It is estimated that up to 10% of patients who develop pancreatic ductal adenocarcinoma have a familial predisposition. In the majority of these families, the genetic predisposition has not been identified. We do know, however, that mutations in the following genes can increase the risk of pancreatic cancer: \textit{BRCA2} (familial breast and ovarian cancer), \textit{PRSS1} (hereditary pancreatitis), \textit{p16} (familial atypical multiple mole and melanoma), and \textit{HNPCC} (hereditary nonpolyposis colorectal cancer).\(^3\)

Distal Bile Duct Cancer (Cholangiocarcinoma)

Distal cholangiocarcinoma is the second most common of the periampullary
adenocarcinomas. Bile duct cancers or distal cholangiocarcinomas are typically grouped into 3 forms based on anatomic origin. Peripheral or proximal bile duct adenocarcinomas arise in the intrahepatic biliary tree. Perihilar cholangiocarcinomas arise near the bifurcation of the right and left bile ducts. Distal cholangiocarcinomas arise in the most distal part of the bile duct from the junction of the cystic duct to the ampulla of Vater. The incidence of cholangiocarcinoma is much less than that of pancreatic adenocarcinoma. Approximately 30% of bile duct adenocarcinomas are diagnosed as arising in the distal bile duct. It is a disease of the elderly, with a peak incidence in the seventh decade of life. Risk factors for the development of cholangiocarcinoma include sclerosing cholangitis, choledochal cysts, hepatolithiasis, and infestation with liver flukes. The common etiologic factor with these conditions is continued long-term chronic inflammation.

**Adenocarcinoma of the Ampulla of Vater**

Ampullary adenocarcinoma is the third most common of the periampullary malignancies. These cancers are slightly more common in males and have a peak incidence in the seventh decade of life. These cancers tend to cause symptoms of obstructive jaundice relatively early in their course, so they tend to be discovered at a smaller size and earlier stage. Additionally, they tend to have less biologic aggressiveness than pancreatic and distal bile duct adenocarcinomas. Several groups have further subdivided adenocarcinomas into various histologic subtypes including pancreatic, biliary, intestinal, and gastric. Patients with the intestinal subtype have much better prognosis than patients with the other subtypes.

**Duodenal Adenocarcinoma**

Duodenal adenocarcinomas are the least common of the 4 periampullary malignancies discussed in this chapter. They are equally prevalent in men and women and have a peak incidence in the seventh decade. These cancers can arise from benign polyps, as in the colon. Patients with duodenal adenocarcinoma, especially if they have multiple polyps, should be ruled out for familial adenomatous polyposis syndromes. Patients with duodenal adenocarcinoma can present with gastric outlet
obstruction and/or with jaundice if it arises right next to the ampulla. Duodenal adenocarcinomas tend to be larger at diagnosis than pancreatic, biliary, and ampullary adenocarcinomas because of the lack of symptoms until significant intraluminal growth. Patients with duodenal adenocarcinoma have much better prognosis, stage for stage, than patients with pancreatic and biliary adenocarcinomas.

DIAGNOSIS AND STAGING EVALUATIONS

Clinical Presentation

The signs and symptoms associated with periampullary and pancreatic tumors tend to be nonspecific, which often contributes to a delay in diagnosis. Presenting symptoms are commonly jaundice and vague mid-epigastric abdominal pain. Unfortunately, by the time such symptoms are manifest, the tumor is often in its late stages, with an estimated 80% of patients presenting with metastatic or unresectable disease. The combination of jaundice (painless or painful) with pruritus, acholic stools, and tea-colored urine in the absence of acute biliary disease is a constellation of symptoms that should prompt the suspicion of a periampullary tumor. Upon further questioning, a history of vague pain and unintended weight loss is often present. Often, a more severe and persistent mid-epigastric pain that radiates to the back indicates a more advanced tumor. Other relatively nonspecific symptoms such as malaise, fatigue, anorexia, indigestion, or early satiety are often noted upon evaluation. Signs of pancreatic insufficiency (malabsorption, frequent fatty or floating stool) would suggest obstruction of the main pancreatic duct, whereas nausea and vomiting would suggest gastric outlet or duodenal obstruction. A quite subtle sign, but one that is now known to be associated with the ultimate diagnosis of pancreatic malignancies, is the rather sudden development of adult-onset diabetes in previously healthy patients in their sixth decade of life.

The location of the tumor will often influence the signs and symptoms of presentation. For example, tumors in the body and tail of the pancreas are more likely to present at a later stage, with larger tumors contributing to more abdominal pain and weight loss. However, tumors that occur within or adjacent to the distal bile duct tend to present at an earlier stage and manifest
as painless jaundice.

Physical exam findings include scleral icterus, jaundice, and skin excoriation from pruritus and scratching. The Courvoisier sign, noted by palpation of an enlarged gallbladder, may be present without peritoneal signs. More advanced disease may include the findings of cachexia, palpable left supraclavicular lymph nodes (Virchow node), palpable periumbilical nodes (Sister Mary Joseph node), and palpable pelvic metastatic disease on a rectal exam (Blumer shelf).

**Laboratory Evaluation**

Patients who present with signs of biliary obstruction are initially evaluated with basic laboratory testing including a complete blood count, electrolytes, liver function tests, albumin, and prothrombin time. If separate testing suggests a periampullary or pancreatic mass, then additional laboratory values that may be useful include tumor markers such as carbohydrate antigen CA 19-9, carcinoembryonic antigen (CEA), or chromogranin A (if a neuroendocrine tumor is suspected).

Extrahepatic biliary obstruction generally results in hyperbilirubinemia with the direct (or conjugated) bilirubin being more elevated than the indirect (or unconjugated) bilirubin. In addition, the alkaline phosphatase is generally more significantly elevated with extrahepatic biliary obstruction than the transaminases (alanine aminotransferase or aspartate aminotransferase). The prothrombin time or international normalized ratio (INR) may be abnormal due to malabsorption of fat-soluble vitamins such a vitamin K. Hypoalbuminemia from malabsorption and weight loss may be present. While the tumor marker CA 19-9 may be helpful, its sensitivity and specificity can be limited by certain conditions. First, the blood test for CA 19-9 is dependent on the Lewis blood group antigen phenotype and is not detectable in patients with Lewis AB– phenotype (approximately 5%-10% of the population). Second, biliary obstruction artificially elevates CA 19-9 levels, and therefore, it is not a reliable tumor marker in the presence of an ongoing obstruction. After relief of the biliary obstruction and subsequent normalization of the bilirubin, CA 19-9 may then become a more reliable tumor marker. Other conditions such as inflammation, cholangitis, and nonpancreatic tumors (gastrointestinal, ovarian) are also associated with increased CA 19-9 levels. Therefore, CA19-9 can support a diagnosis of
periampullary or pancreatic adenocarcinoma but it should not be used to infer the actual diagnosis. An elevated CA 19-9 may be useful for monitoring response to therapy or for monitoring disease progression.

**Imaging Evaluation**

Accurate imaging of periampullary and pancreatic tumors is essential for optimal treatment planning. Well-done imaging provides information about the extent of disease and staging estimation and assists the surgeon in determining the potential for a complete resection. A dedicated, fine-cut, 3-phase pancreas protocol computed tomography (CT) scan provides valuable information regarding local (primarily vascular) and regional (primarily the liver as the most common site of metastasis) spread of disease (Fig. 73-1). Alternatively, for patients with CT contrast allergy or renal insufficiency, a magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) study can provide similar information (Fig. 73-2). In the absence of metastatic disease, attention is paid to the local vasculature that will affect operative planning. Namely, the relationship of the tumor to the inferior vena cava (IVC), portal vein (PV), superior mesenteric vein (SMV), superior mesenteric artery (SMA), celiac trunk, and hepatic artery is assessed. Signs of abutment or invasion of these vessels is not a direct contraindication for resection, but these tumors are considered borderline resectable and the neoadjuvant treatment planning and the operative technique will likely be altered (Fig. 73-3). For locally advanced adenocarcinoma of the pancreas, we favor a neoadjuvant approach to test the biology of the tumor and attempt to downstage the tumor before considering a resection.
FIGURE 73-1 Axial and coronal computed tomography scans demonstrating a resectable tumor in the head of the pancreas (note plastic biliary stent) with clear tissue planes around the superior mesenteric artery and portal vein.
FIGURE 73-2 Magnetic resonance cholangiopancreatography demonstrating an abrupt cutoff in the common bile duct from a tumor in the head of the pancreas. The pancreatic duct is also dilated, giving a strong suspicion of malignancy.
Figure 73-3 Arterial phase cross-sectional computed tomography imaging demonstrating pancreatic adenocarcinoma tumor abutting the superior mesenteric artery and superior mesenteric vein.

Additional imaging with endoscopic ultrasound (EUS) and concomitant fine-needle aspiration (FNA) biopsy can both add valuable information regarding the relationship of the tumor to the mesenteric vessels and simultaneously confirm a tissue diagnosis. Biopsy confirmation is not always necessary for resectable lesions; however, the treatment approaches to neuroendocrine tumors, lymphomas, and other tumors that occur in the periampullary and pancreatic region vary significantly such that biopsy is often warranted.

The routine use of positron emission tomography (PET) combined with CT for periampullary and pancreatic tumors is common, but its ultimate utility is still being debated. The lack of resolution and fine detail around the vasculature is such that the need for a pancreas protocol contrasted CT scan is not obviated. However, PET-CT may be useful in resolving suspicious potentially metastatic lesions noted on other imaging modalities (Fig. 73-4). Despite the use of improved imaging techniques (including PET-CT), small subcapsular liver nodules or occult peritoneal implants are still discovered in approximately 10% to 20% of patients who meet operative
FIGURE 73-4 Positron emission tomography/computed tomography scan demonstrating a focus of discreet hypermetabolic activity in a small lesion of the liver adjacent to the gallbladder consistent with metastatic adenocarcinoma of the pancreas.

Biliary Decompression and Tissue Diagnosis

Jaundice is often the first presenting sign for periampullary tumors prompting further diagnostic and therapeutic interventions. The advantage of endoscopic retrograde cholangiography (ERC) is that it directly evaluates the periampullary region. Periampullary adenomas, adenocarcinomas, or other lesions may be visualized for direct biopsy. ERC may also be useful for diagnosing and treating benign causes of jaundice such as choledocholithiasis or inflammatory conditions such as primary sclerosing cholangitis. At ERC, tumors involving the distal bile duct region often demonstrate an abrupt (as opposed to smoothly tapered) cutoff suggestive of malignancy (Fig. 73-5). The double duct sign (dilation of the extrahepatic common bile duct and the pancreas duct) is most often a sign of malignancy (Fig. 73-6). ERC also
provides the opportunity for biopsy or brushing of the bile duct to obtain a tissue diagnosis. If a definitive diagnosis is not obtained at ERC and is desired for treatment planning, then other approaches such as EUS with FNA or direct cholangioscopic-guided biopsy may be necessary.

**FIGURE 73-5** Endoscopic retrograde cholangiography demonstrating a narrow tapering of the common bile duct secondary to a tumor in the distal bile duct.
The need for biliary stenting depends on staging, the patient’s condition, and the timing of potential surgical resection. Patients with metastatic or locally advanced tumors will benefit from stenting, and the immediate relief from the obstruction allows for the patient’s symptoms to improve while the remainder of the evaluation is conducted. Most patients are grateful for the symptom relief from pruritus, malabsorption, scleral icterus, and changes in stool color, although this can take several days to weeks depending on the degree of acquired liver dysfunction. For patients presenting with resectable disease, the value of routine preoperative stenting is an area of controversy. A recent prospective randomized trial in pancreatic cancer patients presenting with a total bilirubin level of 2.3 to 14.6 mg/dL found that routine preoperative stenting was associated with an increase in serious complications with no change in mortality or length of stay compared to patients who went straight to surgery within 7 days of diagnosis. Select patients with resectable tumors may still benefit from biliary stenting if they
have evidence of cholangitis, intractable pruritus, or significant nutritional deficiencies or if surgery cannot be arranged in a timely (<7 days) fashion.

SURGICAL APPROACHES

Laparoscopy

The use of staging or diagnostic laparoscopy varies significantly from provider to provider and institution to institution. Proponents of the technique argue that it can potentially save some patients from the morbidity of a nontherapeutic exploratory laparotomy. Opponents of routine staging laparoscopy argue that improvements in cross-sectional imaging have significantly reduced the number of patients discovered to have occult metastasis and that the extra cost and inefficient use of operative room time do not justify the added expense. Most high-volume pancreatic and hepatobiliary centers employ a selective approach to staging laparoscopy. The likelihood of finding metastatic disease is relatively greater in patients with larger tumors of the body and tail of the pancreas or patients with markedly elevated CA 19-9 (>200 U/mL).

Whipple Procedure

A potentially curative pancreaticoduodenectomy is the preferred approach to resectable periampullary carcinomas. An upper midline or bilateral subcostal incision is used to gain access to the abdomen. The primary survey for an occult metastatic disease is conducted by exploring the entire abdomen with particular attention to the liver, omentum, peritoneal surfaces, and base of the transverse mesocolon. The secondary survey assesses the involvement of the tumor with the adjacent mesenteric vessels. The exact sequence of secondary assessment may vary depending on preoperative imaging and suspicion of potential vascular involvement; however, a consistent and systematic approach is favored to reduce variability and enhance reliability. The duodenum is mobilized and a Kocher maneuver is performed to assess the relationship of the tumor to the SMA and retroperitoneal structures such as the IVC, right renal vein, and aorta. Following this, the SMV is
located as it courses posterior to the neck of the pancreas. It may be helpful to lift up the transverse mesocolon and follow the middle colic vein until it enters the SMV. The tunnel under the neck of the pancreas is cleared by gentle blunt dissection of the SMV away for the posterior neck of the pancreas. The PV assessment on the superior aspect of the pancreas is generally accessed after first ensuring that the common hepatic artery is clear of tumor involvement. The common hepatic artery is identified coursing parallel and close to the superior border of the pancreatic head. Tracing the hepatic artery leads to the gastroduodenal artery tracking in a caudal direction. The gastroduodenal artery is dissected near its origin from the proper hepatic artery and test clamped to ensure adequate flow through the hepatic artery prior to dividing the gastroduodenal artery. Division of the gastroduodenal artery allows for better visualization of the PV and subsequent creation of a tunnel on the cephalad side of the pancreas neck to connect with the prior SMV dissection from below. At this point, the major vascular structures have been evaluated, and an assessment is made regarding the chances of achieving a margin-negative resection with or without the need for vascular reconstruction. If necessary, the procedure can be abandoned at this juncture since no enteric structures have been divided.

Once the decision has been made to proceed with pancreaticoduodenectomy, a cholecystectomy is performed and the common bile duct is encircled, dissected free, and divided around the level of the cystic duct insertion. The decision to perform a pylorus-preserving versus classic Whipple procedure is contingent on local tumor extent and surgeon preference. Each approach has its relative proponents and opponents. If the tumor is well away from the pylorus, a pyloric-preserving approach may be taken by dividing the duodenum 1 to 2 cm beyond the pylorus with a stapling device. If tumor encroaches upon the pylorus, then a wider margin (classic Whipple) with the division of the stomach to include the antrum with the specimen is undertaken. The right gastroepiploic vessels are divided to allow retraction of the stomach out of the field. The previously dissected tunnel posterior to the neck of the pancreas is reaffirmed, and hemostatic stay sutures are placed along the superior and inferior edges of the pancreatic neck to control bleeding, provide retraction, and facilitate exposure of the SMV. While protecting the SMV, the pancreatic neck is divided sharply so that the main pancreatic duct can be easily identified. A frozen section of the pancreatic duct margin is sent early such that additional pancreatic margins
may be obtained before reconstruction. Cautery is applied to control the small vessels bleeding from the cut edge of the pancreas.

Moving approximately 15 to 20 cm distal to the ligament of Treitz, the jejunum is divided with a stapling device. The proximal jejunum and fourth portion of the duodenum are separated from the root of the mesentery using clips or a cautery device to control the many small vessels going to the jejunum. The intestine to be removed with the specimen is passed posterior to the root of the mesentery and into the right upper quadrant. The attachments from the head and uncinate process of the pancreas are carefully dissected away from the SMV and PV, clipping or ligating small venous branches. The duodenum and uncinate process are rotated out of the retroperitoneum to allow dissection along the lateral border of the SMA. Working in a combination of both anterior and posterior approaches, the final attachments of the pancreas to the SMA and SMV/PV are separated. A search for any additional regional lymph nodes is made to ensure an adequate lymph node dissection. Extensive periaortic and vena cava lymph node dissections are not necessary as they have not been shown to improve survival. The specimen is oriented and marked to facilitate pathologic analysis. Careful examination of the retroperitoneal margin is of crucial importance.

Reconstruction is commenced by passing the divided jejunum either through the transverse mesocolon to the right of the middle colic vessels or posterior to the mesenteric vessels to lay in the right upper quadrant as an upside down “J.” The body of the pancreas is freed from the splenic vein for approximately 2 cm to provide length for the jejunal anastomosis. An end pancreas to side of jejunum anastomosis is prepared for a mucosa-to-mucosa connection. Fine-caliber absorbable suture is used on the mucosa in an interrupted fashion. Although routine pancreatic duct stenting has not been shown to reduce pancreatic fistula rates, in some patients with a soft pancreatic gland or a small pancreatic duct, a pediatric feeding tube may be sized to the pancreatic duct, trimmed to about 6 cm, and fixed in place across the anastomosis. An outer layer of a permanent suture is used on the serosa and pancreatic capsule to buttress the pancreas against the jejunum. The internal pancreatic stent will generally pass unnoticed in the stool several weeks later.

The hepaticojejunostomy is created about 5 to 10 cm away from the pancreaticojejunostomy. Because the common bile duct has often been obstructed, the bile duct is often dilated and fibrotic, thus facilitating the
anastomosis. This is generally performed in a side jejunum to end common bile duct manner, with a duct-to-mucosal anastomosis using a fine absorbable monofilament in either a running or interrupted fashion. If the bile duct was not obstructed, a small internal stent similar to that used for the pancreatic duct anastomosis may also be used. A few buttressing absorbable outer sutures are placed to hold the jejunum in place against the hilum of the liver.

Reconstruction of the stomach or duodenum to the jejunum is accomplished in an antecolic manner about 20 to 25 cm downstream to the biliary anastomosis. This may be done using stapling devices or with a 2-layer hand-sewn technique according to surgeon preference. Closed suction drains are placed around the pancreatic and biliary anastomoses in an effort to control potential biliary or pancreatic fistulae, which are responsible for much of the morbidity and mortality associated with this operation. Figure 73-7 shows the steps of the Whipple operation with reconstruction.

**FIGURE 73-7** Organs removed during Whipple operation and reconstruction: (A) lines of transection on stomach/proximal duodenum, pancreas, and distal duodenum; (B) specimen removed during pancreaticoduodenectomy including, gallbladder, duodenum, distal bile duct, and head of pancreas; and (C) reconstruction with pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy.

**Distal Pancreatectomy**

For cancers of the pancreatic body and tail, a distal pancreatectomy and splenectomy compose the preferred operative approach. For benign conditions of the pancreas or very small neuroendocrine tumors, a spleen-preserving distal pancreatectomy may be considered. The reported advantage
of preserving the spleen is due to the potential risk of postsplenectomy sepsis. However, removing the spleen with the tail of the pancreas simplifies the procedure and reduces the risk of significant bleeding associated with the tedious dissection of the splenic artery and vein along the pancreas. Furthermore, the potential for postsplenectomy sepsis in adults is quite low, and this risk can be further mitigated through the administration of vaccination for pneumococcus, *Haemophilus meningitides*, and *Haemophilus influenzae*. For adenocarcinomas and larger neuroendocrine tumors in the pancreas, including the splenectomy enhances the removal of prognostically relevant regional peripancreatic lymph nodes.

Diagnostic and therapeutic laparoscopy can be very useful for tumors in the body and tail of the pancreas. Access to the abdomen can be made by inserting the laparoscope near the umbilicus for the initial exploration to rule out occult metastatic disease. A decision can then be made to proceed with a resection using laparoscopic techniques or converting to an open approach. Similar operative principles apply to either technique. Depending on the size and location of the tumor, either a midline incision or a left subcostal incision may be selected. The lesser sac is entered and the colon is dissected free from the attachments to the stomach and spleen. The short gastric vessels are divided, and the peritoneal attachments between the posterior stomach and anterior pancreas are opened to allow retraction of the stomach cephalad. The peritoneal attachments on the inferior border of the pancreas are divided, and an assessment of the tumor location and anticipated pancreatic transection are noted. Care is taken to identify and preserve the inferior mesenteric vein as it enters the splenic vein posteriorly near or at the SMV–splenic vein junction. The splenic artery is identified on the superior aspect of the pancreas and traced back to its origin near the celiac trunk. The splenic artery is encircled and a test clamp applied to ensure that there is still adequate flow to the liver through the hepatic artery. Tumors in the body and neck region of the pancreas often track along the splenic artery, so it is important to ensure that a clear margin can be established at the takeoff from the celiac trunk. The artery is intentionally secured and divided first to reduce blood loss. The dissection of the pancreas is conducted from lateral to medial (releasing the splenic attachments and lifting the spleen up with the tail of the pancreas) or from medial to lateral by dividing the pancreatic parenchyma first.

Management of the stump of the pancreas is controversial as a variety of techniques have been employed (eg, stapling device, electrocautery,
harmonic scalpel, direct oversewing of the pancreatic duct, or buttressed compression sutures) without any one technique demonstrating a reproducible reduction in pancreatic fistulae. The splenic vein is divided close to the PV while preserving inferior mesenteric vein inflow. Pancreatic fistula is a common complication (20%-30%), and therefore, a surgical drain is left in place adjacent to the pancreatic stump to control any potential pancreatic leak.

**Palliative Operations**

When patients are discovered to have a metastatic or unresectable disease at the time of operative exploration, it is important to have a good understanding of their symptoms, desires, and estimated life expectancy to inform the decision regarding operative palliation. The additional operative morbidity and mortality must be balanced against estimated life expectancy and the more durable palliation achieved with operative hepaticojejunostomy or gastrojejunostomy. For patients with relatively lower tumor burden and distal bile duct obstruction, an end-to-side Roux-en-Y hepaticojejunostomy provides the most durable intervention for relief of biliary obstruction. The decision regarding the need for relief of potential gastric outlet obstruction can be more challenging because of the vague symptoms often associated with pancreatic head tumors that do not necessarily cause a mechanical obstruction. Furthermore, the published literature regarding gastric outlet obstruction in unresectable pancreatic cancer patients demonstrates a wide range (3%-20%) in the ultimate need for intervention. An antecolic loop gastrojejunostomy is sufficient to allow patients the simple pleasure of being able to eat again. A final consideration for operative palliation is the use of a chemical splanchnicectomy at the time of open operation. The celiac trunk is palpated, and 20 mL of 50% ethanol is injected along either side of the aorta at the level of the celiac plexus with a spinal needle. A prospective randomized trial comparing saline to 50% ethanol injection demonstrated superior pain control at 2 to 6 months in the ethanol group.

**Minimally Invasive Pancreatic Surgery**

**LAPAROSCOPIC PANCREAS SURGERY**
Laparoscopic surgery has become the standard of care for several abdominal operations. The inherent challenges of pancreas surgery, including the retroperitoneal location of the pancreas, proximity to the mesenteric and hepatic vasculature, and the technical challenge of reconstruction, have slowed the acceptance of laparoscopic pancreas surgery and specifically the pancreaticoduodenectomy. However, this is an emerging field that continues to gain acceptance and, in the appropriate clinical scenario, can potentially minimize operative morbidity and blood loss while improving the quality of life. Since the first reported cases of a laparoscopic distal pancreatectomy and a laparoscopic pancreaticoduodenectomy in the 1990s, the acceptance and adoption of these complex minimally invasive operations has increased. There is also a continually growing body of literature that demonstrates that these minimally invasive procedures can offer benefits when compared to their open counterparts. While initial reports argued these operations should be reserved for benign surgical indications, there is now increasing evidence that minimally invasive resections for malignancies not only are feasible but may also reduce morbidity and improve subsequent delivery of adjuvant therapy.

The first laparoscopic pancreaticoduodenectomy was reported in 1994, and as a result of more reports in the literature showing that laparoscopic pancreaticoduodenectomy can be performed safely and with acceptable complication rates, the popularity has been increasing, particularly in the past decade. There have been several retrospective studies that have attempted to compare laparoscopic versus open pancreaticoduodenectomy. Asbun and Stauffer compared a cohort of 53 laparoscopic pancreaticoduodenectomies versus 215 open procedures from 2005 to 2011. In this cohort of patients, the laparoscopic group had significantly less blood loss (1032 vs 195 mL), fewer transfusions (4.7 vs 0.64 units), shorter intensive care unit stays (3 vs 1.1 days), and shorter overall hospital stays (12.4 vs 8 days). Complication rates were similar between the 2 groups. Oncologic outcomes demonstrated that the number of lymph nodes removed was greater for the laparoscopic group (16.84 vs 23.44 nodes) and margin status was equivalent. Operating time was significantly longer in the laparoscopic group (401 vs 541 minutes). Although the cohorts in this study were well matched, if major vascular resection was required, open surgery was performed, adding some selection bias.

Croome and Yamashita went on to look specifically at patients
undergoing resection for pancreatic ductal adenocarcinoma and compared
108 laparoscopic pancreaticoduodenectomies to 214 open resections.
Importantly, these 2 groups were equivalent with regard to tumor size, T
stage, and tumor grade.\textsuperscript{28} When comparing the 2 approaches, they found
similar node resection rates, margin status, and postoperative complications.
Notably, they showed that the laparoscopic cohort required fewer blood
transfusions (19\% vs 33\%) and had a shorter time to initiation of adjuvant
therapy (59 vs 48 days), and there was a significantly higher proportion of
patients in the open cohort (12\%) who had a delay of over 90 days or who did
not receive adjuvant chemotherapy at all compared to the laparoscopic cohort
(5\%). There was no overall survival difference between the 2 groups after a
median follow-up of 16 months, but there was a significant improvement in
progression-free survival in the laparoscopic group. This study clearly
illustrates that in an experienced center, laparoscopic
pancreaticoduodenectomy can be safely performed for pancreatic ductal
adenocarcinoma with comparable oncologic resections. Laparoscopic
resection may also improve outcomes by reducing transfusion burden and
increasing successful delivery of adjuvant therapy, which may have long-
term implications.

\textbf{ROBOTIC PANCREATIC SURGERY}

Robotic pancreatic surgery is another area of growing interest that has not
been studied yet in as much depth as laparoscopic pancreatic surgery. The
first robotic distal pancreatectomy was described in 2003.\textsuperscript{29} Shortly
thereafter, this was followed by the first description of a robot-assisted
pancreaticoduodenectomy in which laparoscopy was used for pancreatic
resection and the robot was used to perform intracorporeal biliojejunal and
gastrojejunal anastomoses. Subsequent refinements of the robotic technique
have resulted in total robotic pancreaticoduodenectomies.

The largest series studying robotic distal pancreatectomies and
pancreaticoduodenectomies originate from the University of Pittsburgh.
Shakir et al\textsuperscript{30} reported a series of the first 100 robotic distal pancreatectomies
performed from 2008 to 2013 at the University of Pittsburgh. In this study,
they identified a learning curve of 40 cases, after which significant reductions
were seen in the operative time (from 331 to 210 minutes) and readmission
rates (from 28\% to 20\%). Boone et al\textsuperscript{31} from this same group reported a
series of 200 consecutive robotic pancreaticoduodenectomies from 2008 to 2014. In this study, a significant learning curve was again reported, with improvements in blood loss and conversion to open surgery after 20 cases (600 vs 250 mL and 35% vs 3.3%, respectively), reduction in incidence of pancreatic fistula after 40 cases (27.5% vs 14.4%), and reduction in operative time after 80 cases (581 vs 417 minutes). In both of these series, the authors demonstrate that after optimization beyond the learning curve, robotic distal pancreatectomies and pancreaticoduodenectomies can be performed with longer operative times but with similar mortality and morbidity rates compared to historical open standards.

To more directly compare robotic versus open pancreaticoduodenectomy, a multicenter study was recently completed comparing perioperative data for patients who underwent robotic (211 patients) versus open (817 patients) pancreaticoduodenectomies. The robotic procedures were performed at centers within the United States that perform a large number of these procedures annually, and only operations performed “after the learning curve” were analyzed. The robotic procedure was found to have longer operative times by 75 minutes, reduced blood loss, and an overall reduction in major complications. However, hospital lengths of stay and readmission rates were equivalent. Future analysis of robotic pancreatic resection that critically appraises the cost-benefit analysis of the robotic platform, quality of life, and long-term outcomes will be important in understanding the future role of robotics in pancreatic surgery.

**Technique**

At our institution, we offer the laparoscopic approach for pancreas surgery for anyone who has a resectable lesion. Relative contraindications include body mass index >35 kg/m$^2$, borderline lesions, and neoadjuvant treatment of cancer.

We start the operation with 5 ports to create a semicircle around the pancreas. After evaluating the abdomen for the absence of metastatic disease in the lesser sac, the hepatic and gastroduodenal arteries are identified. Dissection and ligation of the gastroduodenal artery are done, allowing for orientation and evaluation of the PV below. At this point, attention is redirected to the SMV, along the lower edge of the pancreas in relation to the
previously identified PV. This is followed by the creation of the tunnel underneath the neck of the pancreas. Once completed, the gallbladder is taken down from the gallbladder fossa and used for retraction to allow dissection and transection of the common bile duct. At this point, the ligament of Treitz is dissected and opened by extending our Kocher maneuver. The proximal jejunum is brought through and is then stapled and transected.

Attention is brought back to the right upper quadrant where the distal stomach is stapled and transected. The neck of the pancreas is also transected, paying attention to good hemostasis of the superior and inferior pancreaticoduodenal artery branches. The transected jejunum mesentery is taken down leading to the uncinate process. This leaves an excellent view of the SMA, allowing for transection of the uncinate process right along it.

Finally, the 3 anastomoses are completed, in a similar fashion to the open technique, using intracorporeal knots in either a running or interrupted fashion to the jejunum, which is already in proper position from the previous maneuvers and brought through the previous ligament under the mesenteric vessels. We have found that a pediatric feeding tube for both the pancreas and bile duct facilitates the anastomosis laparoscopically.

POSTOPERATIVE CARE AFTER PANCREAS SURGERY

Pancreatic head resections are complicated procedures with high rates of postoperative morbidity. Rates of postsurgical complications have been decreasing over the past several years, resulting in significant improvement in perioperative mortality. This substantial change can be attributed to multiple factors; nevertheless, a standardized approach to operative technique, postoperative care, refined intraoperative resuscitation, and clear communication between various teams are all critical in our experience.

We consider optimizing intraoperative patient resuscitation a high priority; this consists of formulating a dedicated team of anesthesiologists with a consistent approach to intraoperative resuscitation. Operations performed with minimal blood loss should obviously be resuscitated differently than the rare cases of massive blood loss. Over- or underresuscitation will lead to an increased risk of postoperative complications.

A direct and detailed checkout process between the operating and critical
care teams is important to reduce the risk of any potential miscommunication. We developed a standardized postoperative order set to improve adherence to our postoperative pancreas resection protocol. We familiarized our surgical unit nurses with our postoperative recovery pathway and significantly improved communication between physicians and nurses. We set up regular meetings to continue to improve our intra- and postoperative care.

Our current post-Whipple pathway (Table 73-1) includes close observation in a monitored unit for the first 24 hours. We usually transfer patients to a dedicated surgical nursing unit on postoperative day (POD) 2. Nasogastric tubes are generally discontinued on POD 1 depending on output. Ice chips and sips of water are permitted early on. Aggressive use of incentive spirometers, early ambulation, and tight blood sugar control are critical. The formal introduction of a clear liquid diet usually waits until POD 3 or 4. Regular diet is usually introduced in the next 48 hours. Nausea and vomiting may be rate-limiting steps to advancing diet.

**TABLE 73-1: POSTPANCREATICODUODENECTOMY PATHWAY**
## POD 0 (day of surgery: direct transfer from OR to ICU/transfer to medical floor if no issues)

<table>
<thead>
<tr>
<th>Labs</th>
<th>CBC, CME Mg, Plos, ABG, serum amylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td>SSI, PCEA/PCA, PPL, LR at 150 or as ordered, SQH every 8 h, O2 as per protocol, PO medication okay if no NPO, nasojejunal tube if needed</td>
</tr>
<tr>
<td>Diet</td>
<td>NPO</td>
</tr>
<tr>
<td>Activity</td>
<td>OOB, LAO-T, IS 10 times per hour</td>
</tr>
<tr>
<td>Devices/ tubes</td>
<td>NGT to IWS, JP drains to bulb suction, SCDS, TEDS, Foley</td>
</tr>
<tr>
<td>Physician notes</td>
<td>PT/OTT consult; no CPAP postoperatively; swallow consult</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every hour; PO every 4 h, flush NGT every 6 h with 30 ml</td>
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</tbody>
</table>

## POD 1 (SICU: transfer to surgical specialty in morning if no issues)

<table>
<thead>
<tr>
<th>Labs</th>
<th>CBC, CME Mg, Plos, coagulation tests</th>
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<tbody>
<tr>
<td>Medications</td>
<td>SSI, PCEA/PCA, PPL, LR at 84 or as ordered, SQH every 8 h, uO2 every 8 h, O2 as per protocol, PO medication okay if no NPO, nasojejunal tube if needed</td>
</tr>
<tr>
<td>Diet</td>
<td>Sips/chips ≤250 ml/h</td>
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<tr>
<td>Activity</td>
<td>OOB, LAO-T, IS 10 times per hour; pulmonary toilet</td>
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<tr>
<td>Devices/ tubes</td>
<td>Discontinue NGT unless laparoscopic Whipple (in which case keep in until POD 3); JP to bulb suction; maintain Foley and SCDS while in bed; TEDS</td>
</tr>
<tr>
<td>Physician notes</td>
<td>Discontinue arterial line or central line, if applicable; transfer to floor order in by 8:00 AM with telemetry</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every 4 h; PO every 4 h, patient OOB; all labs checked; flush NGT every 6 h with 30 ml until &quot;OK&quot;; PT/OTT consult</td>
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## POD 2

<table>
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</tr>
<tr>
<td>Diet</td>
<td>Clear liquid diet</td>
</tr>
<tr>
<td>Activity</td>
<td>OOB, LAO-T, IS 10 times per hour; pulmonary toilet</td>
</tr>
<tr>
<td>Devices/ tubes</td>
<td>Discontinue NGT unless laparoscopic Whipple; JP to bulb suction</td>
</tr>
<tr>
<td>Physician notes</td>
<td>Discontinue arterial line or central line, if applicable; transfer to floor order in by 8:00 AM with telemetry</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every 4 h; PO every 4 h, patient OOB; all labs checked; flush NGT every 6 h with 30 ml until &quot;OK&quot;; PT/OTT consult</td>
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## POD 3

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<tr>
<td>Diet</td>
<td>Post-Whipple diet</td>
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<td>Activity</td>
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<td>Devices/ tubes</td>
<td>Discontinue NGT unless laparoscopic Whipple; JP to bulb suction</td>
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<tr>
<td>Physician notes</td>
<td>Discontinue arterial line or central line, if applicable; transfer to floor order in by 8:00 AM with telemetry</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every 4 h; PO every 4 h, patient OOB; all labs checked; flush NGT every 6 h with 30 ml until &quot;OK&quot;; PT/OTT consult</td>
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## POD 4

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<tr>
<td>Diet</td>
<td>Clear liquid diet</td>
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<tr>
<td>Activity</td>
<td>OOB, LAO-T, IS 10 times per hour; pulmonary toilet</td>
</tr>
<tr>
<td>Devices/ tubes</td>
<td>Discontinue NGT unless laparoscopic Whipple; JP to bulb suction</td>
</tr>
<tr>
<td>Physician notes</td>
<td>Discontinue arterial line or central line, if applicable; transfer to floor order in by 8:00 AM with telemetry</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every 4 h; PO every 4 h, patient OOB; all labs checked; flush NGT every 6 h with 30 ml until &quot;OK&quot;; PT/OTT consult</td>
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## POD 5

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<tr>
<td>Diet</td>
<td>Post-Whipple diet</td>
</tr>
<tr>
<td>Activity</td>
<td>OOB, LAO-T, IS 10 times per hour; pulmonary toilet</td>
</tr>
<tr>
<td>Devices/ tubes</td>
<td>Discontinue NGT unless laparoscopic Whipple; JP to bulb suction</td>
</tr>
<tr>
<td>Physician notes</td>
<td>Discontinue arterial line or central line, if applicable; transfer to floor order in by 8:00 AM with telemetry</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every 4 h; PO every 4 h, patient OOB; all labs checked; flush NGT every 6 h with 30 ml until &quot;OK&quot;; PT/OTT consult</td>
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## POD 6 (discharge)

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<td>Medications</td>
<td>SSI, PCEA/PCA, PPL, LR at 84 or as ordered, SQH every 8 h, O2 as per protocol, PO medication okay if no NPO, nasojejunal tube if needed</td>
</tr>
<tr>
<td>Diet</td>
<td>Clear liquid diet</td>
</tr>
<tr>
<td>Activity</td>
<td>OOB, LAO-T, IS 10 times per hour; pulmonary toilet</td>
</tr>
<tr>
<td>Devices/ tubes</td>
<td>Discontinue NGT unless laparoscopic Whipple; JP to bulb suction</td>
</tr>
<tr>
<td>Physician notes</td>
<td>Discontinue arterial line or central line, if applicable; transfer to floor order in by 8:00 AM with telemetry</td>
</tr>
<tr>
<td>Nurse notes</td>
<td>Vitals every 4 h; PO every 4 h, patient OOB; all labs checked; flush NGT every 6 h with 30 ml until &quot;OK&quot;; PT/OTT consult</td>
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</tbody>
</table>

**While previous studies showed no difference between pylorus preservation and classic Whipple operations, we found that transection of the very distal stomach, just above the pylorus, with a wide antecolic gastrojejunostomy reconstruction, has reduced delayed gastric emptying substantially. Delayed gastric emptying is usually self-limited. Nasogastric tube reinsertion may become necessary in the setting of delayed gastric emptying; it is paramount that this is done by experienced personnel sometimes under fluoroscopic guidance to avoid any insertion-related complications. Parenteral nutrition is usually initiated after POD 7 to 10 if there is still no hope for adequate oral intake. Motility agents have been shown to improve gastric emptying after pancreaticoduodenectomy.**

**The Achilles heel of pancreatic resections is pancreatic duct leak (Figs 73-8 and 73-9). A meticulous surgical technique is key to reduce this potentially life-threatening complication. Reported leak rates are highly variable and dependent on definition. Volume-only-based definitions are difficult to interpret. The most commonly used definition compares serum amylase**
levels with drain amylase levels. Surgically placed drains have been shown to decrease morbidity and mortality from pancreas juice leaks. Systemic signs of infection (eg, fever, elevated white blood cell count) on POD 4 to 5 or later should prompt laboratory and radiographic workup. Postoperative abdominal or retroperitoneal fluid collections should raise suspicion for an anastomotic/pancreatic juice leak. These fluid collections should be drained and samples sent for amylase levels and cultures for targeted antibiotic therapy under appropriate circumstances. Pancreatic leaks in the setting of dilated ducts and firm pancreas in pancreatic cancer patients should be low. Patients with small pancreatic ducts and soft pancreas with other types of periampullary cancers (eg, bile duct, ampulla) are at higher risk for an anastomotic leak.

**FIGURE 73-8** Extravasation of contrast from main pancreatic duct.
The need for postsurgical drain placement after pancreaticoduodenectomies has been questioned. Some retrospective studies failed to show a clear benefit to routine drainage. However, a recent prospective, randomized, multicenter study showed that elimination of intraoperative drainage following pancreaticoduodenectomies increases the frequency and severity of complications. Drain placement significantly decreased gastroparesis, intraabdominal fluid collections, intraabdominal abscesses, severe diarrhea, need for postoperative drain placement, hospital stay, and mortality. The data safety monitoring board terminated the study early secondary to the significantly increased mortality in the no-drain group.

We favor intraoperative drain placement as well, because it decreases the
severity of postoperative complications in our experience. Surgically placed drains are routinely tested for amylase levels and compared with serum levels after advancement to regular diet.

A prospective study from Europe found that early drain removal in a selected group of patients could be beneficial, as it was associated with a lower pancreatic fistula rate and decreased abdominal/pulmonary complications, resulting in decreased hospital stay and cost.33

Management of high-output fistulas can be more challenging. Drains should be well secured to prevent accidental removal. Decreasing drain output can be managed with slow, gradual removal of external drains allowing enough time for the tissue around the drain to form a track. In the setting of persistently high drain output, nothing by mouth (NPO) status with total parenteral nutrition should be considered.

The role of octreotide remains controversial. Theoretically, somatostatin and its analogs are decreasing enteric secretions, but systematic reviews have failed to identify significant differences in postoperative mortality. Somatostatin can be helpful in the control of high-output fistulas.

Pasireotide was shown to decrease clinically significant pancreatic fistulas and abscesses in a recently published single-institution randomized clinical trial. Three hundred patients were randomized to receive 900 µg of subcutaneous pasireotide or placebo twice daily for 7 days. The rates of clinically significant postoperative fistulas, leaks, and abscesses were all significantly lower in the pasireotide group after pancreaticoduodenectomies or distal pancreatectomies.34

Postpancreatectomy hemorrhage is a rare but serious postoperative complication. It is frequently associated with a pancreatic anastomotic leak and can present with blood loss via abdominal drains, hematemeses/melena, unexplained hypotension, or as a laboratory finding. Sentinel bleed (small amount of blood in a drain hours before massive hemorrhage) could be a warning sign and has to be taken seriously. The final diagnosis is made via CT scan or angiography (Fig. 73-10). We consider angiography the gold standard (Fig. 73-11). The risk of the dreaded bleeding from the gastroduodenal artery can be minimized with a careful intraoperative management of the gastroduodenal artery stump via double tying or clipping the arterial stump with nonabsorbable suture.
FIGURE 73-10 Postoperative computed tomography scan of intravenous contrast extravasation from gastroduodenal artery stump (marked by arrow).

FIGURE 73-11 A and B. Angiographic image of gastroduodenal artery stump leak before and after coil placement.

Postpancreatectomy chyle leak is infrequent and usually self-limiting. A low-fat diet should be considered in most cases; nevertheless, persistent leak or high-output fistulas should be treated with NPO status and total parenteral
nutrition. A recent consensus statement by the International Study Group on Pancreatic Surgery defined chyle leak as the occurrence of a milky colored fluid output from a drain on or after POD 3 with triglyceride content of greater than 100 mg/mL. Three different grades of severity were defined as follows: grade A, oral dietary restrictions; grade B, prolonged hospital stay, total parenteral nutrition, octreotide, or drain placement; and grade C, intensive care unit admission or mortality.\textsuperscript{35}

**SURGICAL OUTCOMES**

**Postoperative Complications**

Perioperative morbidity and mortality for major pancreatic resections have declined significantly over the past 2 decades. An increasing number of publications have addressed the surgical volume-outcome relationship. There is mounting evidence that complex pancreaticobiliary resections should be performed in high-volume centers to decrease postoperative complications.\textsuperscript{36} The exact definition of a high-volume surgeon or center is debated; however, 10 to 12 cases per year usually qualifies as high volume.

Although postsurgical mortality in high-volume centers is low (0%-3%), postoperative morbidity continues to remain high (30%-50%). The frequent serious postoperative complications are delayed gastric emptying (15%-20%), pancreatic anastomotic leak (10%-20%), wound infection (8%-10%), intra-abdominal (8%-10%) abscess, postoperative hemorrhage (1%-8%), and pancreas fistula (5%).\textsuperscript{18}

The International Study Group of Pancreatic Surgery has greatly contributed to our understanding and better definition of postoperative complications. A series of publications by this group standardized definitions for postpancreatectomy hemorrhage, delayed gastric emptying, and pancreatic anastomotic leakage. Postpancreatectomy hemorrhage has been categorized by 3 important parameters: onset (before or after 24 hours from the time of surgery), location (intra- or extraluminal), and severity (low or high). Delayed gastric emptying has been defined as the inability to return to a standard diet by the end of the first postoperative week. Categories of A, B, and C have been established considering the inability to tolerate solid food by 7, 14, or 21 days or nasogastric tube requirement by 3, 7, or 14 days
Postoperatively or reinsertion of a nasogastric tube between the days mentioned above. Postoperative pancreatic fistula has been defined as drain output of any measurable volume of fluid on or after POD 3 with amylase content greater than 3 times the serum amylase activity, with the following grades established: A (no clinical impact), B (deviation from normal postoperative course, percutaneous drain placement), or C (reoperation or death). Measurable drain output past 3 days with negative drain amylase signals no leak in the majority of patients in our experience.

SURVIVAL, ADJUVANT, AND NEOADJUVANT THERAPY

Survival

Surgically treated periampullary cancers continue to have high recurrence rate and poor overall survival. Only a small minority (15%) of all newly diagnosed patients undergo curative-intent surgical resections. Long-term survival in periampullary cancers is a rare event. A recent paper using a large population-based dataset identified lymph node ratio (number of nodes harboring disease/total number of nodes examined), adjuvant chemotherapy, and pathologic T stage as being the top 3 variables associated with long-term survival in pancreatic cancer patients. Ten-year overall survival in over 11,000 surgically treated patients was 3.9% (Fig. 73-12). The authors developed an easy to use nomogram to help identify potential long-term survival from surgically treated pancreatic cancer (Fig. 73-13 and Table 73-2).

TABLE 73-2: SCORING SYSTEM FOR NOMOGRAM PREDICTING LIKELIHOOD OF 10 YEARS OF SURVIVAL FROM DIAGNOSIS
The presence or absence of nodal disease has been shown to impact survival in multiple previous studies. A recent meta-analysis examined overall survival rates in surgically treated periampullary cancers based on the location of the positive node. Intraoperatively diagnosed nodal disease in a hepatic artery node resulted in no 3-year survivors, compared with a 23% 3-year survival rate in patients with nodal disease and without hepatic artery nodal involvement. Para-aortic nodal involvement discovered intraoperatively resulted in even worse survival rates. These retrospective data suggest that in addition to lymph node ratio, the exact location of nodal involvement has additional significant implications on postsurgical survival in periampullary cancers.38

Autopsy series have suggested that there are 2 major groups of patients with advanced pancreas adenocarcinoma: those who die from bulky metastatic disease and those who die from complications of locoregional tumor recurrence. The first group of patients appears to be much more predominant in our experience. As a result, certain subgroups of patients may benefit from increased intensity therapy locally, whereas other groups may
benefit from increased systemic therapy.

The relative contribution of various treatment modalities to survival in periampullary cancers continues to be debated. Currently, accepted treatment modalities include surgery, chemotherapy, and radiation in various combinations. Preoperative or adjuvant chemotherapy likely meaningfully increases chances of survival, although the benefit is likely on the order of months rather than years.

Large population-based studies continue to show dismal results, with overall survival as low as 13 months, in the setting of curative intent resection for pancreatic adenocarcinoma followed by adjuvant chemotherapy. Even today, selected centers of excellence continue to report median survival times of 24 months or shorter for pancreatic cancer treated with curative intent surgery and adjuvant therapy. This translates into a 5-year survival of about 20%.

Five-year survival of patients with resected invasive ampullary adenocarcinoma is significantly better (40%-50%). Patients with resected distal bile duct cancer seem to be surviving longer than pancreatic cancer patients but shorter than patients with invasive ampullary cancers (25%-30%). Patients with duodenal cancer have 5-year survival rates comparable to patients with ampullary cancers (45%). Surgical margin status and the presence of lymph node metastasis continue to be strong predictors of long-term outcome for all periampullary cancers.

**Adjuvant Therapy**

The benefits of adjuvant chemotherapy and radiation in resected, early-stage periampullary cancers are poorly studied. Earlier published trials lumped various periampullary tumors together or enrolled metastatic and locally advanced patients, making interpretation of these studies difficult. Adjuvant therapy is typically administered 1 to 2 months after surgery. Postoperative complications can delay adjuvant treatment. The best adjuvant chemotherapy combination continues to be debated.

The first adjuvant therapy for pancreas adenocarcinoma dates back to 1985. This small phase III trial randomized patients to receive adjuvant fluorouracil (FU) and radiation versus observation in the postoperative setting. The adjuvant therapy group had a significant survival advantage (20
A phase III European Organization for Research and Treatment of Cancer trial studied adjuvant radiotherapy and FU following curative-intent resection of cancers of the pancreas and periampullary region. Two hundred and eighteen patients were randomized to adjuvant therapy or observation, with over half of the patients having pancreatic cancer. When results were stratified by tumor location, the 2-year survival rate was 63% in the observation group and 67% in the treatment group. Progression-free survival was also similar between treatment groups.

Although gemcitabine showed promise in early clinical trials, it had no survival benefit over FU plus folic acid, with both arms having a median overall survival of 23 months, in the European Study Group for Pancreatic Cancer (ESPAC)-3 trial for surgically resected pancreatic adenocarcinoma. Gemcitabine has been combined with various other drugs in multiple other studies without a significant improvement in overall survival. A more recently published study from Europe compared single-agent gemcitabine (11% response rate) with a combination regimen (FU, leucovorin, irinotecan, and oxaliplatin [FOLFIRINOX]; 31% response rate) in the setting of stage IV pancreatic cancer. Similarly, in the metastatic setting, the combination of nab-paclitaxel plus gemcitabine increased median overall survival by nearly 2 months, compared to gemcitabine alone. Although results from these trials enrolling patients with metastatic pancreatic cancer are not directly applicable to patients with resected pancreatic cancer, early clinical trials and retrospective studies using neoadjuvant FOLFIRINOX in locally advanced pancreatic cancer are encouraging.

The recently presented ESPAC-4 trial showed potentially promising advances in the adjuvant treatment of surgically resected pancreatic cancers. Seven hundred and thirty-two patients were randomized to receive the standard of care (gemcitabine) or gemcitabine plus capecitabine for 24 weeks within 12 weeks of surgery. The median overall survival was 28 months for the combination regimen versus 25.5 months for gemcitabine alone; however, the estimated 5-year survival rates were 28.8% and 16.3%, respectively, for the 2 groups, with comparable rates of toxicities.

The role of radiation in the treatment of periampullary cancers is even more debatable. Because most patients experience recurrence with distant disease, systemic chemotherapy is usually given before radiation.
controversial, prospectively randomized trial studying the effects of radiation in pancreatic cancer from Europe (ESPAC-1) showed potentially detrimental effects of postoperative radiation.\textsuperscript{46} Other retrospective reviews showed potential benefit, but the effects of radiation are difficult to separate from the potential benefits of chemotherapy. Study outcomes have also been scrutinized by the inclusion of patients with positive or unknown surgical resection margin status. Radiation may be best used in the setting of preoperative chemoradiation in pancreatic cancer for concerns of major vessel involvement or for close or involved resection margins in the postoperative setting for periampullary tumors, but the data, especially in ampullary and biliary cancers, are rather sparse.

The Advanced Biliary Cancer (ABC)-02 trial randomly assigned over 400 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin followed by gemcitabine or gemcitabine alone. Median overall survival was 11.7 months in the cisplatin-gemcitabine group compared with 8.1 months in the gemcitabine-only group. While combining cisplatin with gemcitabine appears to be beneficial in locally advanced or metastatic cholangiocarcinomas and ampullary cancers, the trial obviously provides no evidence for its use in resected, early-stage cancers.\textsuperscript{47}

**Neoadjuvant Therapy**

Several studies examined the risks and benefits of neoadjuvant chemotherapy or chemoradiation in the setting of resectable and locally advanced pancreatic cancer. Arguments used for administration of neoadjuvant therapy include the following: high risk of undiagnosed stage IV disease (15%-30%); conversion of locally unresectable disease to resectable disease (15%-40%); preoperative radiation given in well-vascularized tissue may be more effective; preoperative selection tool in patients with marginal candidacy for surgery from a general medical standpoint; increase in margin-negative resection rate; and most patients will receive some form of chemotherapy or radiation (up to 100%), as opposed to the large number of patients having to omit or delay adjuvant therapy secondary to postoperative complications (up to 40%).\textsuperscript{48}

Neoadjuvant therapy remains highly controversial in localized disease,
even for pancreatic cancer, where it has been the most studied. Some investigators reported overall survival of approximately 3 years after administration of neoadjuvant chemoradiation to patients with resectable pancreatic cancer.\textsuperscript{48} This survival time is almost a year longer compared with survival curves reported from other major institutions in the United States\textsuperscript{39} in the setting of curative intent surgery followed by adjuvant therapy. However, these findings are not uniform, and recent meta-analysis of studies addressing potential benefits of neoadjuvant treatment for pancreatic cancer found little to no evidence of survival benefit for resectable or borderline resectable tumors treated in a neoadjuvant fashion. Given all the above, surgically resectable periampullary cancers undergo upfront surgery in our practice.

Neoadjuvant therapy for borderline resectable pancreatic cancer is more accepted. Several societies published papers on their definition of borderline resectable disease, but one could still argue for a more rigorous definition to facilitate comparison of clinical trials and for developing a more homogenous treatment approach. All definitions are based on the relationship of the primary tumor and surrounding important vasculature. The Americas Hepatopancreatobiliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology/National Comprehensive Cancer Network definition of borderline resectable pancreatic tumors includes the following: (1) venous involvement of the SMV/PV demonstrating tumor abutment, encasement, short segment venous occlusion but with suitable vessel proximal and distal to the area of the vessel involvement, for safe resection and reconstruction; (2) gastroduodenal artery encasement up to the hepatic artery and short segment encasement/direct tumor abutment of the hepatic artery with no extension to the celiac trunk; and (3) less than 180-degree involvement of the SMA.\textsuperscript{49} A more recent simplified definition by Cao et al\textsuperscript{50} used a tumor vein circumferential interface grouping (TVI) system, as follows: no interface, <180 degrees of vessel circumference, or >180 degree of vessel circumference or occlusion.

The best neoadjuvant therapy protocols continue to be debated. Several centers, including ours, have used regimens used in clinical trials for stage IV disease with reasonable safety profiles (FOLFIRINOX, nab-paclitaxel, and gemcitabine). Gemcitabine-based chemoradiation protocols have also been studied in clinical trials.\textsuperscript{51} Patients should undergo a thorough clinical and
radiographic reevaluation after neoadjuvant therapy to rule out newly
developed stage IV disease. Surgery should be performed within 4 to 8 weeks
after completion of neoadjuvant therapy. Delaying surgery beyond 3 months
following the administration of neoadjuvant radiation could result in more
challenging operations with potentially further increased risk of
complications secondary to radiation-induced fibrosis in our experience.

We recommend starting neoadjuvant therapy with induction
chemotherapy. This approach spares the potential toxicities of radiation in
that relatively large subset of patients (up to 30%) who develop widespread
stage IV disease while receiving induction chemotherapy. Standard-dose
radiation therapy is 50.4 Gy in 1.8 Gy fractions. However, recent
developments in radiation therapy, such as intensity-modulated radiation
therapy and stereotactic body radiation therapy, have resulted in higher
biological doses and fewer toxicities with potential improvement in
outcomes.

**Immunotherapy**

Immunotherapy is an emerging modality for many cancers such as melanoma
and renal cell cancer. However, its role in pancreatic cancer has yet to be
defined. The purpose of immunotherapy is to activate both the cellular and
humoral immune components of the immune system. It is an attractive
modality because it has a distinct toxicity profile from chemotherapy and
radiation therapy. It can reach all areas in the body and potentially allow for
memory to prevent recurrence. Pancreatic cancer was originally thought to be
poorly immunogenic. However, recent data suggest otherwise. For example,
patients with higher levels of CD4+ and CD8+ tumor-infiltrating
lymphocytes had longer overall survival after surgical resection.

Since 1995, there have been 4 peptide vaccine trials, 2 recombinant
vaccine trials, 1 dendritic cell vaccine, 4 whole cell vaccines, and 1
combination immunotherapy trial. Although encouraging, the results from
single-agent immunotherapy in pancreatic cancer patients have been
disappointing. Because pancreatic cancer is an immune-tolerant tumor, the
treatment strategy requires all modalities: surgery, chemotherapy, radiation,
and immunotherapy. The future of pancreatic cancer immunotherapy lies in
identifying more tumor antigens, targeting multiple antigens, incorporating

checkpoint blockade inhibitors, and tumor microenvironment manipulation. The role will be better understood with continued clinical trials.\(^8\)

**FUTURE DIRECTIONS**

Progress in the neoadjuvant and adjuvant therapy of periampullary cancers has been modest at best. Slight improvements in survival have been observed with the use of various polychemotherapy combinations. To date, new targeted therapies have shown little to no significant impact on survival. Similarly, administration of targeted agents mostly in conjunction with gemcitabine blocking a single pathway in a molecularly unselected patient population has not led to consistent improvements. Strategies involving blockade at multiple levels may be more promising given the complexity of the pancreatic cancer genome. A better understanding of the molecular and genetic pathophysiology of periampullary adenocarcinomas will hopefully open up new treatment opportunities in the future.

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INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs), traditionally termed islet cell tumors, are rare cancers occurring in approximately 1000 patients per year in the United States, representing 3% of all pancreatic tumors.\(^1\) The incidence of neuroendocrine tumors has increased over the last three decades, likely from increased use of and improvement in imaging modalities.\(^2\)\(^−\)\(^4\) The incidence overall of PNETs is increasing from .17 per 100,000 people in 1973 to .47 per 100,000 people in 2007.\(^5\) The peak incidence for PNET is between the ages of 40 and 69 years. While survival is significantly longer than patients with pancreatic adenocarcinoma, once patients have metastatic disease cure is not likely. However, surgical treatment plays a very important role in palliation of symptoms from hormone-producing tumors. Overall survival rate of resected tumors is 55%, but is only 15% with metastatic disease. Surgical resection for localized disease is the only curative treatment. The majority of PNETs are nonfunctional; however, some may secrete active gastrointestinal hormones that produce clinical syndromes. Most tumors are
sporadic; however, some are associated with syndromes such as multiple endocrine neoplasia (MEN), von Hippel–Lindau syndrome, neurofibromatosis, tuberous sclerosis, and von Recklinghausen syndrome. Tumors associated with MEN syndromes are more likely to be aggressive and multifocal.

PNETs have a wide spectrum of biologic behavior. Some are low grade and indolent, while others behave aggressively and have a propensity to metastasize. Some functional tumors are more likely to be benign, such as insulinomas, while others such as glucagonomas are almost always malignant. Tumors may produce multiple hormones complicating the diagnosis. The functional tumors typically produce symptoms related to the dominant hormone that is produced. This chapter reviews the clinical syndromes, workup, and treatment for pancreatic endocrine tumors.

ANATOMY AND PHYSIOLOGY

Endocrine tumors of the pancreas originate from islet cells, hence the traditional name of islet cell tumors. The islets arise from either neural crest cells or embryonic foregut endoderm. They appear histologically similar to carcinoid tumors of the gastrointestinal tract. The tumors are broadly classified into functional and nonfunctional tumors. Nonfunctional tumors compose 40% to 90% of all PNETs and are more common than functional tumors. Functional tumors cause symptoms that are indicative of the hormone the tumor produces. Most commonly these include gastrinomas, vasoactive intestinal polypeptide-secreting tumors (VIPomas), glucagonomas, somatostatinomas, and other rare functional tumors (Table 74-1; Fig. 74-1).

### TABLE 74-1: FUNCTIONAL TUMOR TYPES

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Hormone</th>
<th>Tumor Type</th>
<th>Presentation</th>
<th>Location</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>Insulin</td>
<td>Insulinoma</td>
<td>Whipple triad</td>
<td>Entire pancreas</td>
<td>10%</td>
</tr>
<tr>
<td>Beta</td>
<td>Glucagon</td>
<td>Glucagonoma</td>
<td>Necrolytic migratory erythema</td>
<td>Tail</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Delta</td>
<td>Somatostatin</td>
<td>Somatostatinoma</td>
<td>Diabetes, diarrhea, choledolithiasis</td>
<td>Pancreas, duodenum, small bowel</td>
<td>70%</td>
</tr>
<tr>
<td>G</td>
<td>Gastrin</td>
<td>Gastrinoma</td>
<td>Ulcer disease</td>
<td>Pancreas triangle</td>
<td></td>
</tr>
<tr>
<td>D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>VIP</td>
<td>VIPoma/WDHA</td>
<td>Watery diarrhea, hypokalemia, achlorhydria</td>
<td>Tail</td>
<td>50%</td>
</tr>
</tbody>
</table>
The endocrine portion of the pancreas makes up about 1% to 2% of the gland by weight. Pancreatic islets are composed of four main cell types: alpha cells that secrete glucagon, beta cells that secrete insulin and amylin, delta cells that secrete somatostatin, D2 cells that secrete vasoactive intestinal peptide (VIP), and F cells that secrete pancreatic polypeptide (PP). The distribution of the endocrine cell types varies within in the gland. Beta and delta cells are distributed evenly throughout the pancreas, whereas alpha cells are concentrated in the body and tail, and F cells are mostly in the uncinate process. This has clinical consequence when partial pancreatectomies are performed.

HISTORY

Endocrine tumors of the pancreas were first described by the symptoms a functional tumor would cause. In 1908, the first description of a pancreatic adenoma was described by Nichols, and subsequently Mayo described a
pancreatic islet cell tumor and hyperinsulinemia. This was followed by the Whipple triad in 1935 by Whipple and Frantz. Next, Becker described what would be a glucagonoma when describing a tumor causing dermatitis, anemia, and diabetes. Zollinger and Ellison described an islet cell tumor of the pancreas causing peptic ulcer disease and acid hypersecretion in 1955, and later gastrin was found to be the hormone responsible for this syndrome, known as Zollinger–Ellison syndrome (ZES). VIPomas were described in 1958 by Verner and Morrison, who presented two patients with watery diarrhea and hypokalemia with an associated islet cell tumor. Most recently, secretin has been confirmed as a diarrheogenic hormone from a case first described in 1968 by Zollinger and Ellison.

**GENETIC SYNDROMES**

Multiple endocrine neoplasia type I (MEN-1) is an autosomal dominant inherited disease. MEN-1 is characterized by primary hyperparathyroidism in approximately 90% to 100% of patients with the syndrome. Pancreatic neuroendocrine tumors are next most common, and can be functional or nonfunctional. These are usually nonfunctional. Gastrinomas are the most common functional PNET associated with MEN 1. Pituitary adenomas occur less commonly (20%-65%) as do adrenal tumors (10%-73%) and thyroid adenomas (0%-10%). MEN-1 gene is a tumor suppressor gene that codes for the protein MENIN and is located on chromosome 11q13, and is responsible for this syndrome. Typically, patients with MEN develop tumors at an earlier age than patients without the inherited disorder—usually between 30 and 40 years old.

Suspicion of MEN-1 should be considered when a patient has a family history of endocrine tumors of the pancreas, family members with pituitary or thyroid disease, kidney stones, young age of diagnosis of functional endocrine tumor, endocrine tumor with associated hypercalcemia, or any patient with ZES. Twenty percent of patients with ZES have MEN-1. Genetic screening should be offered to any patient with two or more MEN-1–related tumors, recurrent hyperparathyroidism at a young age, gastrinoma and hyperparathyroidism, or multiple pancreatic neuroendocrine tumors.

Workup of patients with suspected MEN-1 syndrome should include biochemical screening for gastrin, insulin, pancreatic polypeptide, glucagon,
and chromogranin A. In addition, calcium level should be obtained. Hyperparathyroidism should be treated first, before treatment of the pancreatic endocrine tumor. ZES is more difficult to cure in patients with MEN-1, as these tumors are often multiple and can have diffuse hyperplasia of the islets and present with metastasis 50% of the time. Other genetic syndromes such as Von Hippel–Lindau and neurofibromatosis type 1 are also associated with pancreatic endocrine tumors.

NONFUNCTIONAL TUMORS

The majority of pancreatic neuroendocrine tumors are nonfunctional (60%-90%), and many present with distant metastatic disease because they do not have symptoms until late in the course of the disease. Tumors that produce PP, neurotensin, and calcitonin are categorized as nonfunctional, as they do not produce a definable hormonal syndrome. Nonfunctional tumors appear similar on cross-sectional imaging. These tumors are often larger and two-thirds are malignant, while up to 80% have metastasized at the time of diagnosis.

FUNCTIONAL TUMORS

Insulinoma

Insulinomas are the most common functional tumor and occur with an annual incidence of 1 per million patients per year, with the average age at diagnosis of 45 years old. Only 10% of these tumors are malignant. The tumors are located in equal distribution throughout the pancreas. Most are solitary, however when associated with MEN 1 may be multiple. It should be noted that insulinomas rarely occur in MEN 1. These tumors, like most functional tumors, are diagnosed because of symptoms. The Whipple triad classic diagnostic test and includes symptoms of hypoglycemia, plasma glucose less than 50 mg/dL when symptomatic, and relief of symptoms when given glucose (Table 74-2). The neuroglycopenic symptoms are typically headache, lethargy, dizziness, blurred vision, anxiety, excessive sweating, tachycardia, and nervousness. Patients may eat to relieve these symptoms, and as a result
often present with weight gain.

**TABLE 74-2: WHIPPLE TRIAD**

1. Symptoms of hypoglycemia
2. Blood glucose <50 mg/dL
3. Relief of symptoms with glucose

Diagnosis can be confirmed with an elevated insulin-to-glucose ratio greater than 0.3 during fasting, and an associated elevated C-peptide. This ratio can sometimes be found in obese patients but these patients are not hypoglycemic. If the diagnosis cannot be established, a monitored 72-hour fast may be required. The fast should be monitored to prevent life-threatening complications of profound hypoglycemia and to ensure that the hypoglycemia is not factitious. Obtaining sulfonylurea levels and C-peptide may also be necessary if factitious hypoglycemia is suspected. Insulin levels greater than 10 µg/mL and hypoglycemia are very suggestive of insulinomas, however not diagnostic, as these levels of insulin can be seen in other conditions. C-peptide levels greater than 1.2 µg/mL with a glucose less than 40 mL/dL also suggest an insulinomas. The differential diagnosis includes factitious hypoglycemia, chronic adrenal insufficiency, hypopituitarism, nesidioblastosis, and noninsulinoma pancreatogenous hypoglycemia (NIPH). Nesidioblastosis is not associated with a tumor but patients with this do manifest symptoms of hypoglycemia.

Resection is the mainstay of treatment for insulinomas (Fig. 74-2). Preoperative hypoglycemia should be managed with frequent small meals. Octreotide is not typically useful and should be used cautiously, as it can worsen hypoglycemia by suppressing the secretion of glucagon. Diazoxide can also be used to suppress the secretion of insulin. Enucleation is an option for resection of insulinomas given the majority are not malignant. Localization of insulinomas can sometimes be difficult due to the small size of these tumors, averaging 1.0 to 1.5 cm. CT or MRI is usually sufficient to locate the tumor, but endoscopic ultrasound is often a useful adjunct. Determining the relationship of the lesion to the pancreatic duct can help in planning the operative approach. Insulinomas that are in close proximity to
the duct may lead to a pancreatic leak if an enucleation is performed, and a more formal pancreatic resection may be indicated if this is a concern. Intraoperative ultrasound can be used if there has been difficulty in identifying the tumor during the surgery, and again may help in determining the location of the pancreatic duct. If the tumor is not located using these methods, blind resection is not indicated. With current imaging techniques and endoscopic ultrasound, angiography or selective portal venous sampling for insulin levels is used rarely. Injection of calcium into the celiac and superior mesenteric arteries can also further increase the sensitivity of this test.

**FIGURE 74-2** Distal pancreatectomy and splenectomy for insulinoma.

**Gastrinoma**

ZES was initially described in 1955 in two index cases of refractory ulcer disease and diarrhea. The mean age at diagnosis is 50 years, with most cases diagnosed between the ages of 20 and 60 with a male predominance (60%). Those with MEN-associated gastrinomas typically present at a younger age. It is important to consider the diagnosis of MEN-1 in patients with ZES, as 20% of them will have MEN-associated disease. Frequently, gastrinomas are not recognized at the initial clinical presentation and are therefore often
managed incorrectly. Symptoms that should raise suspicion of a gastrinoma include idiopathic peptic ulcer disease or longstanding diarrhea. The high acid load delivered to the duodenum inactivates pancreatic enzymes, causing malabsorption and diarrhea; thus the diarrhea is relieved by nasogastric suction. The liver is the most common site of metastases, with 70% to 80% of patients diagnosed with liver metastases at the time of diagnosis.

Confirmation of a gastrinoma can be made with a fasting serum gastrin level. A fasting serum gastrin greater than 1000 pg/mL is virtually diagnostic for ZES. This must be drawn while that patient is off protein pump inhibitors (PPIs) for 72 hours prior to the test. Gastrinomas do not secrete gastrin to normal stimuli such as amino acids and peptides or gastric distention. The normal inhibition of gastrin by low luminal pH does not occur, and secretin causes stimulation rather than inhibition of gastrin. Other medical conditions can also cause hypergastrinemia, thus serum gastrin by itself is not diagnostic of ZES. Pernicious anemia, atrophic gastritis, and the use of proton pump inhibitors all can cause elevation of serum gastrin and achlorhydria. Acid hypersecretion and hypergastrinemia may be found with many conditions such as \textit{Helicobacter pylori} infection, gastric outlet obstruction associated with peptic ulcer, retained antrum, short gut syndrome, or renal failure. A secretin stimulation test can confirm ZES by measuring serum gastrin level after the intravenous injection of 0.4 µg/kg of secretin (Fig. 74-3). Patients can remain on PPIs during this test. Gastrin levels will increase by 200 pg/mL in patients with ZES. A rise in gastrin level by greater than 110 pg/mL over baseline is considered a positive test. Imaging with CT or MRI should be performed to locate the tumor.\textsuperscript{23} EUS is very sensitive for detection as is somatostatin scintigraphy using \textsuperscript{111}In-DTPA-DPhe1 octreotide.\textsuperscript{24} Ninety percent of gastrinomas are located in the gastrinoma triangle (Passaro triangle), which is bounded by cystic duct, the junction of the second and third portions of the duodenum, and the junction of the neck and body of the pancreas (Fig. 74-4).
FIGURE 74-3 Secretin stimulation test. Response of serum gastrin to IV secretin in various conditions. Zollinger–Ellison syndrome will increase by at least 110 pg/mL. The paradoxical response is maintained in patients taking proton pump inhibitors. There is no increase in gastrin over baseline in patients with achlorhydria or with elevations of gastrin secondary to PPI treatment. ZE, Zollinger–Ellison; PA, pernicious anemia; PUD, peptic ulcer disease; PPI, proton pump inhibitor.
FIGURE 74-4 The gastrinoma triangle—the anatomic triangle in which approximately 90% of gastrinomas are found. The gastrinoma triangle is defined by the cystic duct, the junction of the second and third portion of the duodenum, and the neck/body of the pancreas.

Treatment includes resection of the primary tumor (Figs 74-5 and 74-6). In patients may undergo exploration with intraoperative ultrasound to help locate the tumor if no imaging test has identified the lesion preoperatively. When unable to locate the gastrinoma preoperatively the surgeon should undergo a thorough intraoperative search to locate the gastrinoma including a wide Kocher maneuver, which allows for palpation of the head and uncinated of the pancreas, mobilization of the body and tail, intraoperative ultrasound and lastly duodenotomy and exploration of the duodenal mucosa. The duodenum is the most common location of gastrinomas typically in the first or second portion. The mucosa should be inspected carefully as the tumor can be <2 mm and can be multiple. After the duodenum the pancreas is the next
most common location. Intraoperative ultrasound may be useful to locate the
tumor as they can be multiple. If a pancreatic tumor is identified
duodenotomy should be undertaken given the possibility of a second tumor
which be present in as many as 50% of cases.

![Intraoperative Photograph](image)

**FIGURE 74-5** Intraoperative photograph after distal pancreatectomy and
splenectomy showing the cut edge of the pancreas and the splenic vein
stump.
Patients with MEN-1 associated gastrinomas are rarely cured with surgery. Their hyperparathyroidism should be addressed with subtotal parathyroidectomy or total parathyroidectomy and autotransplant of parathyroid tissue. This helps reduce serum gastrin by removing the stimulation from the elevated calcium. Patients with MEN associated ZES with negative imaging should not undergo exploration as cure is rare because of development of metachronous primary tumors owing to the underlying syndrome. Although a low cure rate is to be expected, some studies have still shown prolonged survival.\textsuperscript{25,26} Surgeons that advocate surgical intervention in MEN-related gastrinomas typically would consider the Thompson procedure.\textsuperscript{27,28} This includes a distal pancreatectomy, enucleation of tumors in the head, a duodenotomy and exploration of the duodenum with resection of any duodenal tumors as well as a portal lymph node dissection.\textsuperscript{29} For patients with tumors greater than 2 to 2.5 cm in size surgery is recommended. Ellison et al. reported on 106 gastrinomas 26 of which were MEN related. Those that underwent complete resection had a 10 year disease-specific survival of 100% compared to 40% for an incomplete resection. Despite these results serum gastrin levels remained elevated in 94% of these patients.\textsuperscript{30}
VIPoma

Vasoactive intestinal peptide secreting tumor (VIPoma) was classically described as the WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria). Patients can have over 10 liters/day of diarrhea even when fasting and this has been described as pancreatic cholera. These tumors are extremely rare with an incidence of 1 in 10,000,000 population. Fasting VIP levels can reach nearly 1000 pg/mL in most cases but above 200pg/mL is suggestive of VIPoma. Localization with CT or MRI imaging or octreotide scan is the most common. Fifty percent of these tumors are metastatic at diagnosis and commonly are located in the tail of the pancreas. When treating a VIPoma correction of electrolyte abnormalities must be completed prior to surgical intervention. Octreotide can be useful for symptom control prior to surgery. Resection for palliation is sometimes undertaken to help control symptoms, but this likely does not impact long term survival.

Glucagonoma

Glucagonomas are also very rare with an incidence of less than 1 per 10,000,000-20,000,000 population. The tumors are 2 to 3 times more common in women than men. At presentation, they are usually larger than other PNETs with an average size of 5-10 cm at diagnosis. These tumors arise from alpha cells and a found more often in the body and tail which is were more alpha cells are located. A minority of these tumors are MEN-1 related (5%-17%). Similar to other MEN-related PNETs, these patients tend to present earlier and 60% of patients present with distant metastatic disease at diagnosis.

Two-thirds of patients with glucagonomas present with a characteristic rash called necrolytic migratory erythema and this can be the first symptom of the glucagonoma. The rash is severe, with raised, scaly, erythematous patches on the perineum, trunk and extremities. They also typically present with diabetes, anemia, stomatitis, weight loss, and diarrhea. Dermatologist are often the first to recognize this syndrome. The “four D’s” are often used to describe this constellation of symptoms associated with glucagonoma: diabetes, dermatitis, DVT, and depression. The diagnosis of glucagonoma is confirmed by fasting serum glucagon levels greater than 1000 pg/mL. CT
or MRI is commonly used to locate the tumor.

**Somatostatinoma**

Somatostatinomas are even rarer with less than 100 ever reported and were first described in 1977.\(^{34}\) Patients with somatostatinomas typically present with diabetes, cholelithiasis, diarrhea, and steatorrhea. Somatostatin inhibits insulin, cholecystokinin (CCK) and pancreatic enzyme secretion thus causing the associated diabetes, cholelithiasis, and diarrhea.\(^{35}\) Somatostatin level greater than 100 pg/mL are diagnostic. Seventy percent of these tumors are metastatic and large at diagnosis. They are most commonly found in the pancreas but can be found in the duodenum and small bowel. Localization is typically easily accomplished with cross-sectional imaging given their large size.

**Other Functional Tumors**

Many other rare functional tumors have been described including adrenocorticotropin-producing tumors (ACTHoma), parathyroid hormone-related peptide (PTH-RP), secretinoma, Gastrin releasing factor, calcitonin, enteroglucagon, CCK, gastric inhibitory peptide, luteinizing hormone, neurotensin or ghrelin.

**IMAGING**

Cross-sectional imaging with CT or MRI should be the first step in locating the PNET. Insulinomas and gastrinomas are more difficult to localize with standard imaging because of their small size. PNETs typically have a vascular blush giving them a characteristic enhancement that is helpful in identification and differentiation from other pancreatic tumors or cancer. (Fig. 74-7) Many PNETs express the somatostatin receptor and thus somatostatin-receptor scintigraphy (SRS) (octreotide scan) can be used to image these tumors. If a tumor is unable to be located with CT or MRI, SRS is 80% sensitive in locating the tumor. The sensitivity for insulinomas is less than 50% owing to the fact that the tumor cells frequently lack the somatostatin 2 receptor. SRS is a sensitive imaging technique; however, it is
only able to show the location of the tumor within several centimeters. Endoscopic ultrasound (EUS) is also an alternative imaging technique if CT or MRI hasn’t revealed the location of the tumor. Biopsy is also able to be accomplished at the time of EUS. The sensitivity of EUS to localize small PNETs has been shown to be as high as 97% compared to CT (85%) or MRI (70%).36 (Fig. 74-8) Angiography can be utilized to localize tumors that are small and unable to be localized by CT, MRI, SRS, or EUS. Angiography can localize up to 70% of small tumors (<5 mm) with a characteristic blush. Selective portal sampling for the hormone in question can also be done to help localize the tumor when other methods have failed. Provocative testing is also described but only used currently when the above tests have failed to localize the tumor and there remains a high level of clinical suspicion that the patient has a functional PNET. This is called arterial stimulation venous sampling (ASVS) and is performed by injecting calcium or secretin into the celiac and superior mesenteric arteries followed by sampling from the inferior vena cava for the appropriate hormone in question. (Fig. 74-9) If all imaging tests have been performed and negative exploration and intraoperative ultrasound may be warranted, however, blind resection is not warranted in the majority of cases.
**FIGURE 74-7** CT scan of nonfunctional pancreatic endocrine tumor in the body pancreas.

**FIGURE 74-8** Endoscopic ultrasound of gastrinoma in the tail of the pancreas.

**FIGURE 74-9** Selective secretin arterial stimulation.

68G Ga-Dotatate positron emission tomography (PET) CT seems to be an excellent imaging modality for PNETs and may be the imaging modality of choice. With availability of positron emitting tomography in recent years, PET tracers labeled somatostatin analogues have been developed rapidly.
PNETs demonstrate high uptake of 68 Ga DOTATATE because neuroendocrine tumors express a significant number of somatostain 2 receptors.

**INTRAOPERATIVE IMAGING**

Few advances in imaging techniques over the past several decades have advanced the surgical management of PNETs. Given the difficulty in preoperative localization of these tumors novel intraoperative imaging techniques have been developed. Hall et al. have described using a combined intraoperative portable large field of view gamma camera and a handheld gamma detection probe for $^{111}$In-pentetrotide radioguided localization and confirmation of gastrinoma in 5 patients. They were able to detect additional tumor foci in 3/5 patients with this imaging technique (Figs 74-10 and 74-11).
FIGURE 74-10 Intraoperative imaging—preoperative injection of $^{111}$In-pentetreotide.
SURGICAL CONSIDERATIONS

Localized

Surgical resection is the only curative treatment for pancreatic endocrine tumors. Small tumors can sometimes be enucleated in select cases. Insulinomas are sometimes amenable to this approach. Laparoscopic or robotic resections are becoming more common at experienced institutions. Generally pancreatic head tumors less than or equal to 2 cm may be
enucleated unless the pancreatic duct is involved. Intraoperative ultrasound may help in making this determination. Pancreatic head tumors greater than 2 cm usually require pancreaticoduodenectomy. Tumors in the tail usually require distal pancreatectomy with splenectomy. However with small insulinomas distal pancreatectomy with splenic preservation is an acceptable oncologic operation as the majority are benign. This is not the case with the other functional tumors that are considered malignant in the majority of cases. As noted, tumors less than 2 cm are usually resected, but in the patient with significant comorbidities and with patient preference close observation may be warranted as small tumors are less likely to metastasize. Close follow-up is required in these cases. The goal of surgical intervention is to obtain negative margins even if adjacent organs need to be resected. Liver metastasis should also be removed at the time of operation if feasible. Consideration of cholecystectomy if the surgeon anticipates the future use of octreotide.

**Metastatic**

The quality and length of life is often dictated by the disease burden in the liver. Debulking of functional tumors can be effective palliation of symptoms, but patient selection must carefully weigh the risk and benefit and whether symptoms can be controlled with medical management and is employed less often given other ablative treatment options. For non-functional tumors complete resection of both the primary and liver metastases is the goal. Combination of liver resection and ablative therapies may be used to clear the liver of metastatic disease. As more effective systemic therapies are approved, resection may be more commonplace even in the setting of metastatic disease. Liver-directed therapy using transarterial chemoembolization or surgical resection has been shown beneficial in asymptomatic patients with >25% liver tumor burden. Transarterial chemoembolization (TACE) or bland transarterial embolization (TAE) and radionuclide-laden spheres (yittrium-90) are effective therapies, as the tumors derive most of their blood supply from the arterial circulation. These therapies are often able to stabilize tumor growth and palliate symptoms due to hormonal production.

Peptide receptor radiation therapy (PRRT) is not currently available in the United States, however, shows some promise in treating metastatic PNETs by
delivering a cytotoxic dose of radiation therapy directly to the tumor.

**SYSTEMIC TREATMENTS**

**Somatostatin Analogs**

Somatostatin analogs such as octreotide and lanreotide have been shown to prolong progression-free survival and are thought to stabilize tumor growth in addition to relieving symptoms associated with functional tumors.  

**Targeted Therapy**

Targeted therapies have shown great promise in the treatment of PNETs. Both everolimus and sunitinib are FDA-approved treatments for advanced pancreatic endocrine tumors. A randomized controlled trial of everolimus, an oral inhibitor of mammalian target of rapamycin (mTor) showed an increase in progression-free survival from 4.6 months to 11.0 months. Sunitinib, a multitargeted tyrosine kinase inhibitor, has also been shown to increase progression-free survival to 11.4 months from 5.5 months for placebo, and to increase overall survival in patients with metastatic unresectable disease. Although both have been shown to increase progression-free survival, response rates by RECIST criteria are low. There are no current data for the use of these agents in the adjuvant setting.

**Cytotoxic Chemotherapy**

Cytotoxic chemotherapy currently used for PNETs includes streptozocin-, 5FU- or temozolamide-based regimens. Streptozocin was the first cytotoxic agent described with efficacy in pancreatic endocrine tumors. In comparison with the targeted therapies, the objective response rates with cytotoxic agents have been greater. Capecitabine and temozolamide have been shown to have a high and durable response in PNETs in a small study. Seventy percent of patients had a radiographic response, with median progression-free survival of 18 months. Given this radiographic response, this regimen has also been reported in the neoadjuvant setting.
CONCLUSIONS

Management of pancreatic endocrine tumors requires a multidisciplinary team and a thorough understanding of the biological behavior to determine optimal treatment and surgical therapy. Surgical resection continues to be the only curative therapy. Newer imaging techniques may help identify tumors intraoperatively, as small tumors remain difficult to image with standard CT or MRI. Debulking of metastatic disease continues to play an important role in control of symptoms due to hormone production. Liver-directed therapies such as TACE or Y-90 can also stabilize disease and provide symptom relief. Systemic therapies have shown promise by increasing progression-free survival but have not lengthened overall survival. Patients with MEN-associated PNETs often have multifocal and more aggressive disease, thus if surgical resection is entertained these factors must be considered.

REFERENCES


Drs. Gajdos, McCarter, Edil, Paniccia, and Schulick provide an extremely comprehensive chapter on the evaluation and treatment of patients with cancer of the periampullary region and especially the pancreatic head (Chapter 73). Importantly, there has been a tremendous advance in both the understanding of the molecular biology of pancreatic cancer as well as our ability to accurately image the pancreas and periampullary region prior to surgery. Advances in computed tomography (CT) and magnetic resonance imaging (MRI) have allowed for accurate assessment of critically important tumor-vessel relationships. Such accurate assessment of the relevant anatomy is important for both pretreatment staging and for planning the operation, especially if vascular resection and reconstruction may be indicated. The ability to preoperatively classify patients as having resectable, borderline resectable, or locally advanced pancreatic cancer (LAPC) allows for optimal treatment sequencing (often including neoadjuvant therapy), the evaluation of
patients for investigator-initiated and cooperative group clinical trials, and the referral of patients to higher volume centers.\(^1\) Indeed, to the extent that outcome is improved for patients with localized disease at high-volume centers (by high-volume surgeons), patients will need to be accurately staged (CT imaging) and, when necessary, have biliary stents placed safely in order to facilitate referral to a specialty center. The ability to perform endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) biopsy will prevent diagnostic uncertainty and allow for medical oncology consultation and multidisciplinary care.

Fortunately, the past decade has witnessed the development of consensus for the CT staging of pancreatic cancer. In an attempt to clarify the anatomy of resectable, borderline resectable, and locally advanced disease, Varadhachary and colleagues from The University of Texas M.D. Anderson Cancer Center proposed an objectively defined, CT-based classification that distinguishes borderline resectable pancreatic cancer from both resectable pancreatic cancer and LAPC.\(^2\) This definition was developed for the conduct of clinical trials of neoadjuvant treatment sequencing and was not intended to support a surgery-first strategy for patients who may require vascular resection and reconstruction. The Varadhachary definitions also assumed the technical capability to resect and reconstruct the superior mesenteric–portal vein (SMPV) confluence (when necessary) and that the major determinants of margin status (R status) were the tumor-artery (celiac, hepatic, and superior mesenteric artery) relationships. In contrast to the management of resectable and borderline resectable pancreatic cancer, surgery has typically not been applied to patients with locally advanced or metastatic disease. Patients with LAPC were considered to have inoperable tumors; surgery was felt not to be technically possible. With recent improvements in response rates for systemic therapy, an increasing number of patients with LAPC are found to have stable or responding disease after a prolonged course of systemic therapy (4-6 months or more) with or without having received radiation therapy. Such patients have only 1 site of measurable disease—the primary tumor—and therefore are often sent for surgical consultation to consider removal of the only remaining abnormality seen on cross-sectional imaging. The patient is often confused: Surgery was initially thought not to be possible, and now there is a difference of opinion? In an effort to add clarity to the goals of treatment for patients with LAPC, we recently described a system for categorizing locally advanced disease based on the
tumor-vessel anatomy\textsuperscript{3,4}; in LAPC type A, surgery may be considered after systemic therapy and chemoradiation, and in LAPC type B, surgery will likely never be possible (Table 75-1).

<table>
<thead>
<tr>
<th>Vascular Structures That Determine the Stage of Disease for Localized Pancreatic Cancer</th>
<th>Resectable</th>
<th>Borderline Resectable</th>
<th>Locally Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor-artery anatomy (relationship)</td>
<td>SMA (usually pertains to a tumor of the head or uncinate process)</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>$\leq 180$ degrees (abutment)</td>
</tr>
<tr>
<td>Celiac artery (usually pertains to a tumor of the pancreatic body)</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>$\leq 180$ degrees (abutment)</td>
<td>$&gt;180$ degrees (encasement) but does not extend to the aorta and amenable to celiac resection (with or without reconstruction)</td>
</tr>
<tr>
<td>Hepatic artery (usually pertains to a tumor of the pancreatic neck/head)</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>Short segment abutment/encasement without extension to celiac artery or HA bifurcation</td>
<td>$&gt;180$-degree encasement with extension to celiac artery and amenable to vascular reconstruction</td>
</tr>
<tr>
<td>Tumor-vein anatomy (relationship)</td>
<td>SMV-PV</td>
<td>$\leq 50%$ narrowing of SMV, PV, SMV-PV</td>
<td>$&gt;50%$ narrowing of SMV, PV, SMV-PV\textit{ with a distal and proximal target for reconstruction}</td>
</tr>
</tbody>
</table>

Potential for successful resection after neoadjuvant therapy (%) | 90 | 75 | 60 | 25

Abbreviations: HA, hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SMV-PV, superior mesenteric-portal vein.


For surgeons who recommend a surgery-first strategy to patients with localized, potentially resectable pancreatic cancer, the CT definition of what should be considered “resectable,” and for which immediate surgery may be considered, is becoming more limited, which is a logical response to the clinical observation that almost all patients with apparent operable pancreatic cancer have radiographically occult micrometastatic disease. In general, there is an increasing trend for the management of localized pancreatic cancer with systemic therapy first.\textsuperscript{5-7} Most clinical trials incorporate a period of induction.
systemic therapy, especially in those with arterial abutment, to include 2 to 4 months of chemotherapy, which may be followed by chemoradiation. Emerging clinical trials, as well as off-protocol therapy, include (as a backbone of therapy) what has been proven successful in metastatic disease, such as gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel (Abraxane) and FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin).\(^8\) Our management of localized, operable pancreatic cancer is evolving toward a total neoadjuvant approach (4-6 months) with surgery considered after all intended systemic therapy and chemoradiation. Restaging is performed after each 2 months of therapy; if there is significant treatment response (eg, clinical, radiographic, biochemical [cancer antigen 19-9]), then additional chemotherapy is prescribed with careful follow-up every 2 months. In the setting of stable or, hopefully, responding disease after 4 months of chemotherapy, a transition to chemoradiation is usually recommended. Importantly, our treatment algorithm incorporates a stepwise evolution of treatment that starts with accurate staging and proceeds to an extended course of chemotherapy, followed by chemoradiation and, finally, surgical resection. In the absence of disease response, the chemotherapy regimen can be changed (eg, FOLFIRINOX to gemcitabine plus nab-paclitaxel or vice versa). The length of induction systemic therapy, the timing and dose of radiation therapy, and the use of a variety of biomarkers to assess the presence or absence of response are areas of active investigation. Although chemotherapy and chemoradiation do not increase the risk for pancreatic leak or other known surgery-associated complications, it is likely that some patients of advanced age cannot tolerate multiple treatments in series and thus may not be suitable surgical candidates at the time of posttreatment/preoperative restaging; such patients likely receive a greater oncologic benefit from induction therapy than they would from a surgery-first/surgery-only approach.

Probably the most important technical aspect of pancreaticoduodenectomy is the dissection of the superior mesenteric artery (SMA). In general, exposure of the SMA is facilitated by complete mobilization of the SMPV confluence to the patient’s left. This allows for careful separation of the uncinate process from the jejunal branch of the superior mesenteric vein and, ultimately, exposure of the SMA. Our current understanding of the pathophysiology of local recurrence after pancreaticoduodenectomy (with or without multimodality therapy) is microscopic infiltration of the autonomic
neural sheath that surrounds the SMA (and celiac/hepatic arteries). Adenocarcinoma of the pancreas has a predisposition to spread along neural tissue, and this is likely responsible for the high frequency of local recurrence. As our systemic therapies become more effective, local recurrence may become a more dominant pattern of failure.

CYSTIC NEOPLASMS OF THE PANCREAS

The chapter by Drs. Pucci and Yeo (Chapter 75) is equally comprehensive in their superb discussion of cystic neoplasms of the pancreas. They focus predominantly on serous cystadenoma, mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN). With regard to serous cystadenoma, this histology demonstrates fascinating tumor biology. As mentioned by the authors, it is generally felt that serous cystadenomas do not have the biologic ability to metastasize to distant organs or regional lymph nodes. However, they can be locally invasive and erode into adjacent bowel (duodenum, transverse colon, stomach) and occasionally can obstruct the splenic vein (resulting in sinistral portal hypertension) or the superior mesenteric and/or portal veins (resulting in extrahepatic portal hypertension). Importantly, the diagnosis of (microcystic) serous cystadenoma can usually be made on high-quality CT imaging with or without the additional benefit of EUS due to its characteristic imaging appearance (unless the serous cystadenoma is macrocystic). When referring a patient for EUS to confirm a diagnosis of serous cystadenoma (the EUS appearance is often diagnostic), we would recommend an FNA biopsy if the EUS is not consistent with this diagnosis or there appears to be discrepancy between CT or MRI imaging and the EUS appearance. A biopsy is often needed only when the imaging findings are not all congruent and inconsistent with a diagnosis of serous cystadenoma. Serous cystadenomas are characterized by a cyst fluid carcinoembryonic antigen (CEA) level that is usually undetectable or very low (<5 ng/mL). At present, the diagnosis of a serous cystadenoma is usually not difficult; however, knowing when to intervene with surgery is often challenging. As patients age and operative risk (medical comorbidities) increase, the benefit of surgery in an otherwise asymptomatic patient may be low. For example, it is relatively easy to understand a recommendation for surgery in an otherwise completely healthy 60-year-old patient with a serous cystadenoma of 6 cm or greater. However, the same pancreatic tumor in a
75-year-old patient with 1 or 2 coronary stents and a relatively sedentary lifestyle is not the correct approach. In our practice, we try to carefully weigh risk versus benefit in asymptomatic patients. In addition, for serous cystadenomas that are less than 4 to 5 cm in size, we usually require that they demonstrate growth, over a period of observation, prior to proceeding with surgery; there simply is no down side to this approach. Our underlying philosophy is to completely avoid surgery-related mortality and major morbidity in patients who are asymptomatic with a tumor histology (such as serous cystadenoma) that poses no risk for distant metastases.

As emphasized by Drs. Pucci and Yeo, ovarian stroma is required to secure a diagnosis of MCN and differentiate it from IPMN (in women). However, ovarian stroma is appreciated on histologic assessment of the resected specimen and therefore is a diagnosis made after operation. It is impossible to preoperatively differentiate an MCN from a unifocal branch duct IPMN in a woman. However, MCNs occur in the pancreatic body and tail and are exceedingly rare in the pancreatic head or uncinate process. We would consider an MCN in the pancreatic head or uncinate process to represent an IPMN. Although the relationship between size of the MCN and malignant potential is perhaps not as well studied as with IPMN, in the absence of a solid component or mural nodule (which represent clear indications for surgery), presumed MCNs less than 3 cm in diameter will rarely harbor invasive cancer. Management of such small presumed MCNs is often based on the size of the cyst and the age or medical comorbidities of the patient. For example, after an EUS-FNA biopsy consistent with a mucinous neoplasm in a woman with a single, 3-cm cystic neoplasm in the body or tail of the pancreas that is otherwise normal in appearance (main pancreatic duct not dilated), the decision to proceed with surgery versus observation is typically based on the age and medical comorbidities of the patient. What remains controversial is the surgical approach to MCNs of presumed low malignant potential. If we imagine for a moment that the woman with a 3-cm, FNA-proven MCN in the proximal pancreatic body (mucinous nature of the cyst fluid has been confirmed) is 50 years old, surgery would typically be recommended because of the patient’s young age and the knowledge that such an MCN is premalignant. The contemporary question relates to the recommended form of operation—middle segment pancreatectomy, distal pancreatectomy (with or without splenic preservation), or enucleation. In patients without cancer, we do need to pay more attention to preservation of
islet cell mass in an effort to avoid the intermediate- and long-term complications of insulin-dependent diabetes (in addition to lifestyle changes and risk of hypoglycemia). Our choice for operation in this patient would be a middle segment pancreatectomy with pancreaticogastrostomy for the distal pancreas and coverage of the proximal pancreatic transection site with a falciform ligament pedicle flap. This would hopefully minimize the risk for anastomotic leak, preserve islet cell mass, and ensure that the lesion is completely excised with negative margins. We have not yet adopted enucleation as a routine part of our practice when dealing with mucinous (premalignant) neoplasms.

When dealing with patients who have presumed IPMN, especially those with branch duct disease, the International Consensus Guidelines (formerly Sendai criteria) have now been widely incorporated into clinical practice. As noted by the authors, use of these guidelines will result in a slightly more conservative approach to surgery than may otherwise be the case. By definition, low-risk patients would be treated with at least a period of observation until the size of the cyst or the CT characteristics prompt surgical intervention. Such a strategy is designed to avoid surgery and its associated risk for mortality and morbidity in patients with small cystic neoplasms who have no chance of harboring an invasive cancer. In our practice, enucleation would rarely be considered because we do not operate on cystic neoplasms that would be considered most appropriate for enucleation (those of very low risk). However, the increasing use of cross-sectional imaging has resulted in many more patients being diagnosed with cystic neoplasms of the pancreas. Is it reasonable to consider a lesser procedure (enucleation or endoscopic ablation) for smaller branch duct IPMNs that are diagnosed in younger patients? Is there a role for enucleation or ablative therapies in patients in whom the risk for invasive carcinoma is approaching zero? This is an area of active investigation and frequent discussion at national meetings.

Fortunately, when dealing with a patient who has IPMN and requires surgery, the need for total pancreatectomy is uncommon. If the right or left side of the pancreas requires resection, we commonly send the pancreatic transection margin for frozen section analysis. Work from our group and others has demonstrated that it is probably unnecessary to chase a margin with low-grade dysplasia (pancreatic intraepithelial neoplasia 1 [PanIN-1]) because this can result in the unnecessary resection of additional pancreas. Importantly, at many institutions, there is only modest expertise in the
interpretation of frozen section evaluation of pancreatic transection margins. Surgeons should be cautioned to avoid overaggressive resection of grossly normal pancreatic parenchyma based on frozen section evaluation of pancreatic transection margins, especially when dealing with IPMN. Another area of operative and technical challenge includes IPMNs (often combined main duct/branch duct) involving the neck of the pancreas, should one resect the right or the left side of the gland or perform a middle segment pancreatectomy? In this situation, we would typically divide the pancreas to the right of the neoplasm at the junction of the head and neck of the pancreas. We would then send this margin for frozen section evaluation prior to committing the patient to an extended distal pancreatectomy (in those cases where middle segment pancreatectomy is not preferred). When performing an extended distal pancreatectomy, one needs to be certain that the proximal pancreatic transection margin will be negative, especially if the patient could also be treated with an extended pancreaticoduodenectomy, and thereby preserve some islet cell mass. In general, the preservation of islet cell mass does facilitate improved blood sugar control even if not obviating the need for insulin. This is especially important in patients with limited resources and modest family support in whom a hypoglycemic episode could be life threatening. Finally, it is important to note that patients who undergo surgery for IPMN (in contrast to those who undergo pancreatectomy for MCN) do require long-term follow-up. We typically obtain a baseline MRI of the abdomen 2 to 4 months after surgery, and our next scan would typically occur 1 year later. If there is no evidence of an abnormality in the remaining pancreas, our MRI interval is in the range of 12 to 24 months depending on the histology of the previous resection and the age and general health of the patient.

ENDOCRINE TUMORS OF THE PANCREAS

As described by Drs. Dillhoff and Ellison (Chapter 74), pancreatic neuroendocrine tumors (pNETs) are usually low- to intermediate-grade tumors arising from the pancreatic islets. They are also known as pancreatic endocrine tumors, islet cell carcinomas, and pancreatic carcinoid tumors. The current preferred nomenclature is pancreatic neuroendocrine tumors, or pNETs. The biology of this class of tumors is both unique and fascinating. For example, why do sporadic, nonmetastatic insulinomas virtually never
develop distant recurrence and only very rarely recur locally (virtually all local recurrences are secondary to incomplete enucleation)? Metastatic insulinoma is rare, and when seen, it is always synchronous at the time of diagnosis; we have not seen a case of metachronous metastases. In contrast, patients with multiple endocrine neoplasia type 1 (MEN1) who have nonfunctioning pNETs have a risk of metastatic spread that appears to be related to the size of the primary tumor in the pancreas. Patients with primary tumors less than 2.5 cm in size rarely have associated liver metastases. When weighing the risk of long-term insulin-dependent diabetes with the risk for distant metastases, we often observe small (<1.5 cm) nonfunctioning pNETs in young MEN1 patients. Further, why does the biology of patients with Zollinger-Ellison syndrome differ based on whether the primary tumor is in the pancreas or the duodenum, and what determines where the tumor arises? Equally mystifying is why duodenal gastrinomas are so small, often less than 1 cm in diameter, and rarely associated with liver metastases. Gastrinomas, when located in the pancreas, are usually found within the pancreatic head or uncinate process (gastrinoma triangle), and those 3 cm in size and larger are frequently associated with liver metastases. Consistent with the biology of duodenal gastrinoma, patients with carcinoid tumors of the duodenum almost never have synchronous or metachronous liver metastases even though lymph node metastases are very common. Indeed, the biologic explanation for the varied metastatic potential of functioning and nonfunctioning pNETs is an area of active investigation.

When evaluating a patient with hypergastrinemia, it is important to remember that the major cause of hypergastrinemia is parietal cell dysfunction resulting in achlorhydria and pernicious anemia. Such patients can be differentiated from those with Zollinger-Ellison syndrome by the absence of gastric acid production. In the outpatient center, placement of a nasogastric tube with aspiration of gastric juice for pH testing will easily make this diagnosis. We frequently see patients who have elevated serum gastrin levels either from concomitant administration of a proton pump inhibitor or because of parietal cell dysfunction. A pancreatic or duodenal gastrin-producing tumor is a much less frequent cause of hypergastrinemia. Importantly, consistent with the optimal operative management of virtually all pNETs, regional lymphadenectomy is an essential part of the operative procedure for patients with gastrinoma. Patients with functioning or nonfunctioning pNETs can have persistent or recurrent disease in regional
lymph nodes in the absence of liver, bone, or lung metastases. Careful attention to regional lymphadenectomy is an underemphasized and very important component of the surgical management of patients with pNETs.

Patients with insulinoma virtually always have an insulin level greater than 3 µIU/mL (usually >6 µIU/mL) when the blood glucose is less than 40 to 45 mg/dL and an insulin-to-glucose ratio of ≤0.3, reflecting the inappropriate secretion of insulin at the time of hypoglycemia. It is critically important to confirm the diagnosis of insulinoma by allowing the glucose to decline to less than 45 mg/dL (at which point, the patient is usually symptomatic) and observing the relief of symptoms with the administration of glucagon. Glucagon (1 mg intravenously) is associated with an elevation of serum glucose of approximately 20 mg/dL. The reversal of hypoglycemia with glucagon confirms that hypoglycemia is insulin mediated. In contrast to gastrinomas, which usually occur in the duodenum and pancreatic head/uncinate, insulinomas may develop anywhere throughout the pancreas and do not arise in the duodenum. In the absence of MEN1, the overwhelming majority of insulinomas are unifocal. As previously mentioned, if metastatic disease is not seen at the time of diagnosis, metachronous distant metastases from a presumed benign insulinoma do not occur. However, if the insulinoma is incompletely enucleated, a local recurrence can develop; such local recurrences may not occur for years after the primary operation. When we perform an enucleation of a benign insulinoma, we typically use bipolar forceps, and we are extremely careful to avoid violation of the tumor capsule. The advantage of bipolar cautery is that the operative field remains dry and one can appreciate the junction of the tumor capsule and the normal pancreatic parenchyma. Because the pancreas is highly vascular, it is critically important to keep the operative field as dry as possible. Proper technique for enucleation is much more important than whether the operation is done laparoscopically or open. In the event of a pancreatic fistula, the presence or absence of an abdominal incision becomes insignificant. When an enucleation is performed, the anatomy of the primary tumor in relation to the pancreatic duct should be appreciated on preoperative imaging, and if needed, this important anatomic relationship can be confirmed with intraoperative ultrasound. If one performs a very large enucleation or injures the pancreatic duct, a Roux-en-Y limb of jejunum can be used to create a pancreaticojejunostomy. For large defects in the pancreas, we have made liberal use of Roux-limbs for internal drainage.
With regard to MEN1, all at-risk patients should undergo genetic testing. In addition to MEN1, pNETs can occur in association with tuberous sclerosis, neurofibromatosis, and von Hippel-Lindau (vHL) syndrome. As previously mentioned, there is a defined association between tumor size and risk for liver metastases in MEN1 patients with nonfunctioning pNETs. Balancing the risk for insulin-dependent diabetes with the risk for metachronous liver metastases is indeed a difficult challenge. In our practice, the timing of pancreatic surgery in MEN1-associated nonfunctional pNETs is based on the age of the patient, the size of the pancreatic tumors, and sometimes the tumor biology seen within the family (frequency of metastases and death secondary to metastatic pNET); this latter characteristic may or may not be helpful because biologic heterogeneity within kindreds is well described. We strive to limit the operations performed in MEN1 patients to 2 over the course of their lifetime. In the first operation, we remove either the right or left side of the pancreas (sometimes a lesser procedure) depending on which side of the pancreas can be partially or fully cleared of obvious tumors with local enucleations if needed. The goal is to limit oncologic risk (metastatic disease) and preserve islet cell function (avoid insulin dependence) for as long as possible. If the first operation occurs at a young age, we expect metachronous recurrence in the remaining pancreas in the future, at which time a completion total pancreatectomy may be necessary. However, one would hope that the second operation to complete the total pancreatectomy would not occur until many years after the first operation, thereby avoiding insulin dependence until later in life, at which time the long-term complications of type 1 diabetes are less likely. Because the natural history of MEN1-associated pNETs becomes clear only after decades of follow-up, we still have much to learn in the management of these patients.

Importantly, the past decade has witnessed an explosion in the understanding of the biology of pNETs, imaging technology, and the development of targeted therapies. In 2016, the US Food and Drug Administration approved gallium-68–dotatate for clinical use and the gallium-68–dotatate positron emission tomography (PET)/CT scan has revolutionized the ability to image small pNETs. Most clinicians are now appreciating the understaging of disease that occurred in the era before dotatate imaging. How to use this information responsibly is the current challenge because, in some patients, small-volume disease may pose less risk to length and quality of life than do aggressive interventions. Tyrosine kinase
inhibitors, such as sunitinib, and the mammalian target of rapamycin (mTOR) inhibitor everolimus have shown activity in patients with metastatic pNETs and have stimulated renewed interest in translational research and novel therapies for this disease. Peptide receptor radionuclide therapy (PRRT) with lutetium-177–dotatate is also emerging as an effective therapy for properly selected patients with neuroendocrine tumors. Importantly, many patients who develop metachronous recurrence years after pancreatectomy for a nonfunctioning pNET will have somewhat indolent disease. The majority of these patients will be treated with somatostatin analogue therapy (lanreotide), and disease stabilization is frequently seen with this treatment. The optimal management of patients with low-volume metastatic pancreatic neuroendocrine carcinoma requires thoughtful multidisciplinary input from oncologists, interventional radiologists, and frequently surgeons. Liver resection, systemic therapy (to include lanreotide), PRRT, and local ablative therapies, both intra-arterial and percutaneous, can all add to improved length and quality of life for affected patients; however, their optimal sequencing is critically important.

Finally, in our practice, we rarely proceed with surgery in a patient with a nonfunctioning pNET if a gross, complete resection cannot be performed. However, in the setting of known metastatic disease or a large, borderline resectable primary tumor, we frequently use neoadjuvant therapy (cytotoxic and/or biologic). In the setting of synchronous liver metastases, a 1- or 2-stage surgical approach can be used with or without neoadjuvant therapy. In contrast to exocrine pancreatic cancer, we frequently resect neuroendocrine liver metastases. When dealing with a resectable primary tumor and resectable liver metastases, we usually remove the pancreatic tumor first; if the pancreatectomy goes well, then some or all of the liver disease can be addressed at the same operation. If the magnitude of surgery required for the pancreatic primary is too large, the liver surgery should be performed at a second stage. As one can imagine, there are various degrees of complexity with regard to combined pancreas-liver resections. For patients with more advanced liver metastases, in whom a future liver remnant can be cleared at the time of the initial pancreatectomy, one can even consider portal vein embolization and second-stage extended hepatectomy. This of course assumes excellent health of the patient, a reasonable age category, and the absence of medical comorbidities. Indeed, future options to combine novel systemic therapies with advanced surgical techniques hold great promise for
patients with pNETs, even those with disease that may have been considered
nonoperable in the past.

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INTRODUCTION

Pancreaticoduodenectomy

Perhaps one of the most technically challenging abdominal surgeries, pancreatectomy has evolved from a bold innovative intervention to a well-refined lifesaving procedure over the past decades. Pancreatectomy is, however, associated with a long history of high mortality and morbidity. In 1899, William S. Halsted performed the first successful resection of ampullary carcinoma through a transduodenal approach at Johns Hopkins Hospital. In this surgery, he reimplanted the common bile duct and pancreatic duct onto the duodenum, but did not resect the head of pancreas. The first true pancreatectomy did not occur until 1912, when the German surgeon Walther Carl Eduard Kausch performed the first two-stage pancreaticoduodenectomy with an en bloc resection of the head of pancreas for ampullary carcinoma. Mortality was as high as 25%, and mostly resulted from postoperative hemorrhage, peritonitis, and pancreatic fistula.
The transduodenal approach to pancreatectomy continued to be the approach of choice until 1935. In that year, Allen O. Whipple from Columbia University published his first three cases of the two-stage pancreaticoduodenectomy for ampullary carcinoma (Whipple et al., 1935). Whipple described oversewing the pancreatic stump in order to avoid disruption of the pancreaticojejunostomy. Of the three patients in this report, one died during the immediate postoperative period, one died of anastomotic leak a few months later, and the other suffered from pancreatic fistula but survived. Whipple later modified the pancreaticoduodenectomy into a one-stage procedure. Alexander Brunschwig from the University of Chicago is credited, though, as the first to perform a one-stage procedure to resect a pancreatic head cancer. In 1941, Whipple reported his experience with 41 cases of pancreaticoduodenectomy, emphasizing the importance of one-stage procedure to avoid inflammatory adhesions from a two-stage resection along with an end-to-side choledochojejunostomy and jejunoojejunostomy for prevention of reflux cholangitis (Whipple, 1941).

From the 1940s to the early 1970s, the mortality from pancreaticoduodenectomy remained at least 25% in most series. The one exception was a report by Dr. John M. Howard in 1968, in which 41 cases of pancreaticoduodenectomy were performed without any mortality at the Hahnemann Hospital (Howard, 1968). With the advent of preoperative risk stratification improved imaging, high-volume pancreatic surgery centers, and interventional radiology, the mortality has decreased significantly, to below <2%. In 1990, Dr. Michael Trede from Heidelberg published the experience of 118 consecutive pancreaticoduodenectomies without mortality (Trede et al., 1990). In 1997, Charles Yeo et al. published the experience at Johns Hopkins Hospital with 650 pancreaticoduodenectomies and an overall mortality of 1.4%. Despite these improvements in mortality and the expansion of the indications for a variety of pathologies, the morbidity remains high to this day, ranging from 25% to 45% at most centers. These complications include pancreatic fistula (PF), delayed gastric emptying (DGE), post-pancreatectomy hemorrhage (PPH), biliary leaks, and pancreatic insufficiency. General complications nonspecific to pancreatectomy such as wound infections, sepsis, cardiac and pulmonary events, and renal failure have significantly decreased.
**Distal Pancreatectomy**

Distal pancreatectomy for resection of tumors in the body or tail of the pancreas developed at a slower pace than pancreaticoduodenectomy, largely due to its associated pathology. Carcinoma of the pancreas has been very difficult to diagnose historically—especially the lesions located in the body or tail of the pancreas, since these patients usually present later, manifesting metastatic disease. With improved imaging and the recognition of other entities like pancreatic neuroendocrine tumors, cystic neoplasms, and intraductal papillary mucinous neoplasm (IPMN), distal pancreatectomy has become a more frequent procedure.

The German surgeon Werner Körte reported that Trendelenburg performed perhaps the first reported distal pancreatectomy for sarcoma in the tail of the pancreas in 1882. The patient died after a few months. Theodor Billroth performed the first successful distal pancreatectomy with resection of the most of the body and tail of the pancreas in 1884. Since then there were not many reported cases of this procedure until the 1910s. John M.T. Finney from John Hopkins Hospital reviewed 16 cases of pancreatectomy from the literature and also reported one case of his own. In the 16 reviewed cases, four cases appeared to be distal pancreatectomy for a variety of pathologies and included the 1882 Trendelenburg case (Finney, 1910). His own case was actually a central pancreatectomy for pancreatic cystadenoma. This case was complicated postoperatively by pancreatic fistula that eventually resolved, and the patient survived. In 1913, William J. Mayo from the Mayo Clinic reported one case of distal pancreatectomy with the resection of the body and tail of the pancreas for a benign pancreatic cyst (Mayo, 1913). Keith D. Lillemoe published in 1999 the experience of 235 cases of distal pancreatectomies at Johns Hopkins Hospital (Lillemoe et al., 1999). The mortality was less than 1% but the morbidity was 30%. The most common complications were new-onset diabetes, pancreatic fistula, intraabdominal abscess, small bowel obstruction, and postoperative hemorrhage. Other studies have reported pancreatic fistula as being the most common complication in as many as 25% of patients.

**Total Pancreatectomy**

The most radical pancreatic resection is the total pancreatectomy, and this
was first performed in 1944 by James T. Priestly from Mayo Clinic to remove an insulinoma (Priestley et al., 1944). Alexander Brunschwig also reported the first case of total pancreatectomy for carcinoma in 1944 (Brunschwig, 1944). The concept of total pancreatectomy became popularized in the 1960s and 1970s in order to prevent the high recurrence of pancreatic cancer after partial resection, which was thought to be from a multicentric disease. In addition, surgeons believed that the rate of pancreatic fistula was unacceptably high, and removing the entire gland would obviate this concern. However, studies in the 1980s demonstrated that total pancreatectomy carried the same oncological outcome as partial resection (Karpoff et al., 2001; Schnelldorfer et al., 2008; Sperti et al., 1997; Westerdahl et al., 1993). One reason is that total pancreatectomy does not increase the rate of a negative resection margin compared to partial pancreatectomy. In addition, most pancreatic fistulae can be managed medically without significant long-term complications, negating one potential benefit of total pancreatectomy.

The mortality of total pancreatectomy has decreased significantly over the years. In reports published since 1980s, the mortality ranges from 0% to 17% (Balcom et al., 2001; Karpoff et al., 2001; Swope et al., 1994) in high-volume centers. Total pancreatectomy carries significant endocrine and exocrine sequela that require preoperative evaluation and patient education along with lifelong management of this inherent pancreatic insufficiency. The concerns and risks of diabetes can be potentially mitigated with concurrent islet cell autotransplantation for patients undergoing resection for benign conditions such as chronic pancreatitis. However, a long-term follow-up study from the University of Minnesota has shown that 46% of patients became insulin-dependent again after 5 years despite initial insulin independence immediately after surgery (Sutherland et al., 2012).

In this chapter, we discuss the major complications from pancreatectomy: PF, DGE, PPH, biliary leak, and pancreatic insufficiency. These complications can significantly delay patient recovery, the initiation of adjuvant chemoradiotherapy, and impact patients for years following resection. Progress in the understanding and management of these complications has been made. The International Study Group of Pancreatic Surgery (ISGPS) has significantly contributed to these areas and has formulated consensus definitions and grading of PF, DGE, and PPH.
COMPLICATIONS FROM PANCREATECTOMY

Pancreatic Fistula

Pancreatic fistula is one of the most common and feared complications from partial pancreatectomy and occurs generally in 10% to 25% of cases. The most common clinical presentation is the appearance of murky fluid in a drain left next to the pancreaticoenteric anastomosis or cut edge of the pancreas. Alternatively, the patient manifests an intraabdominal fluid collection of pancreatic juice or abscess following the operation. Historically there have been many different names for this complication, such as pancreatic leak and pancreatic anastomotic insufficiency. The ISGPS has determined these terms as interchangeable and prefers the use of the term “pancreatic fistula” (Shukla et al., 2010).

ETIOLOGY

Pancreatic fistula often results from the disruption of the pancreaticoenteric anastomosis either from ischemia, erosion by pancreatic enzymes, or other technical issues. Pancreatic fistula can also develop from the cut edge of the pancreas if the pancreatic duct has not been sufficiently ligated with suture or controlled with staples.

RISK FACTORS

The texture of the pancreas appears to be the most important risk factor of pancreatic fistula after pancreatectomy. A soft pancreas does not hold suture or staples well, and postoperatively the local inflammatory process can disrupt these. Soft glands are often found in patients with neuroendocrine tumors, ampullary tumors, and cystic lesions. In patients with chronic pancreatitis, the nature of this disease process leads to inflammation and fibrosis of the pancreas, making the gland firm, and the occurrence of pancreatic fistula is relatively low (Donahue and Reber, 2015). Pancreatic cancer is associated with a fibrotic pancreas and this is responsible for a lower PF rate in patients with this disease. Other risk factors include the size of the pancreatic duct diameter and intraoperative blood loss. The ISGPS has posted an on-line risk calculator to help inform the risk of developing a
fistula following resection (https://www.pancreasclub.com/calculators/isgps-calculator/).

**CLINICAL PRESENTATION**

Most commonly, patients with a pancreatic fistula simply demonstrate a change in the character of the effluent found in a surgically placed drain. The fluid no longer appears serosanguinous and instead becomes cloudy or completely clear. Some patients will manifest systemic signs ranging from a prolonged ileus or an elevated white blood cell count with a fever to more ominous signs of a significant inflammatory response with tachycardia, renal dysfunction, and mental confusion. The surgeon should be suspicious of the occurrence of a PF, checking for these changes each postoperative day.

**DIAGNOSIS**

The criteria to diagnose a pancreatic fistula have varied considerably in the literature. A widely used criteria is fluid output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume on or after postoperative day 3 with an amylase content greater than three times the upper normal serum value. Abnormal-appearing drainage other than clear pancreatic juice can also be a sign of pancreatic fistula. In the literature, there are at least four widely used criteria, summarized in Table 76-1 (Bassi et al., 2005).

**TABLE 76-1: DEFINITIONS OF PANCREATIC FISTULA**

1. Output >10 mL/d of amylase-rich fluid (>3× serum amylase) postoperative (postop) day 5 or for >5 days
2. Output >10 mL/d of amylase-rich fluid after postop day 8 or for >8 days
3. Output between 25 mL/d and 100 mL/d of amylase-rich fluid after postop day 8 or for >8 days
4. Output >50 mL/d of amylase-rich fluid after postop day 11 or for >11 days

In 2005, the ISGPS released a report to categorize pancreatic fistula into three grades: grade A (mild), grade B (moderate), and grade C (severe). This system was modified recently and the details are outlined in Table 76-2.

**TABLE 76-2: GRADES OF PANCREATIC FISTULA FROM ISGPF**

<table>
<thead>
<tr>
<th>Main Parameters for POPF Grading</th>
<th>Biochemical Leak</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical conditions</td>
<td>Well</td>
<td>Often well</td>
<td>Ill appearing</td>
</tr>
<tr>
<td>Specific treatment</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes</td>
</tr>
<tr>
<td>US/CT (if obtained)</td>
<td>Negative</td>
<td>Negative/positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Persistent drainage (after 3 weeks)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reoperation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Death related to POPF</td>
<td>No</td>
<td>No</td>
<td>Possibly yes</td>
</tr>
<tr>
<td>Signs of infections</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sepsis</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Organ failure</td>
<td>No</td>
<td>No</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>


Imaging is not required to diagnose pancreatic fistula; however, it may be helpful to assess the size and location of the potential intraabdominal abscess, placement of the surgical drain, and the existence of complications that lead to gastric outlet obstruction from anatomical abnormalities.

**TREATMENT**

The treatment of pancreatic fistula is mostly conservative, and fortunately, most pancreatic fistulae (70%-82%) will resolve within weeks with conservative management. This is true for both pancreaticoduodenectomy and distal pancreatectomy.
With biochemical leak pancreatic fistula, which is the most common form of pancreatic fistula, the patients can still feed orally. Total parenteral nutrition (TPN) or somatostatin analog such as octreotide is not required and this class of fistula rarely delays hospital discharge. In contrast, grade B pancreatic fistula requires significant adjustment from the standard clinical pathway. The patient may require strict NPO and TPN. Octreotide may be indicated if the volume is significant. If the patient has fever or leukocytosis, antibiotics are also needed. Hospital discharged is likely to be delayed as these patients may need interventional drainage of fluid collections or angiographic embolization for hemorrhage, and readmission is more likely to occur. However, the patient can often be discharged home with surgical drain in place and followed up in an outpatient setting.

Grade C pancreatic fistula requires major changes of the standard clinical pathway. The patient often requires NPO, TPN, intravenous antibiotics, and somatostatin analog and care in an intensive care unit. CT scan may show peripancreatic fluid collection. Hospital stays are often lengthened. If the patient continues to deteriorate clinically, reoperation may be required to repair or revise the pancreaticoenteric anastomosis. In extreme conditions, completion pancreatectomy may be necessary.

**PREVENTION**

Over the years, there have been many studies on potential methods to prevent pancreatic fistula. Fibrin glue and other hemostatic agents have been tested. One of the early trials by Kram et al. (1991) has shown promising results. In their report, no pancreatic fistula occurred in 15 patients. However, late reports consistently failed to show the advantage of fibrin glue (Lillemoe et al., 2004; Orci et al., 2014). For example, Lillemoe et al. (2004) reported that out of 125 patients, pancreatic fistula occurred in 26% of the fibrin-glue group, compared to 30% of the control group. A variation of this method, by internal occlusion of the pancreaticojejunostomy anastomosis, also failed to find a significant difference in the incidence of pancreatic fistula (Lorenz et al., 1988).

A double-blinded randomized clinical trial by Allen et al. (2014) from Memorial Sloan-Kettering Cancer Center has shown promising results with pasireotide for prevention of pancreatic fistula. Pasireotide is another somatostatin analog with higher half-life and better binding capacity than
octreotide. Pasireotide or placebo is administered subcutaneously twice daily for 7 days after pancreatectomy. The authors found significant decrease in pancreatic fistula in the pasireotide group compared to the placebo group (9% vs 21%).

**Delayed Gastric Emptying**

DGE is characterized by oral intolerance, inability to remove the nasogastric tube, and/or the necessity of reinserting the nasogastric tube several days after the operation. It can significantly delay the patient recovery, nutritional improvement, and the initiation of adjuvant therapy. In most reports, the rate of DGE ranges from 19% to 57%. (Martignoni et al., 2000; Miedema et al., 1992; Richter et al., 2003; Wente et al., 2007a; Yamaguchi et al., 1999; Yeo et al., 1997).

**ETIOLOGY/RISK FACTORS**

The mechanism of DGE is largely unknown. It has been postulated that the resection of duodenum can trigger DGE, and this is supported by the fact that there is less DGE with duodenum-preserving pancreatic head resection. In addition, distal pancreatectomy that does not involve duodenal resection rarely causes DGE. Decreased motilin level has also been suggested to trigger DGE, given that the prokinetic drug erythromycin, which is a motilin agonist, can reduce the incidence of DGE.

Pylorus-preserving pancreaticoduodenectomy is one of the most common variations of the classic pancreaticoduodenectomy, and some reports have claimed that it is associated with higher incidence of DGE, while others have shown the opposite. The etiology of this may be that pylorus-preserving pancreaticoduodenectomy can cause devascularization or denervation of the pylorus with subsequent pylorospasm.

**CLINICAL PRESENTATION**

DGE is frequently manifested as failure to tolerate PO intake, failure to remove nasogastric tube, or emesis after removal of nasogastric tube.

**DIAGNOSIS**
There have been many definitions of DGE historically. In order to reconcile the difference, the ISGPS has released a consensus definition of DGE in 2007 and also classified DGE into three grades, as shown in Table 76-3.

**TABLE 76-3: THE ISGPS DEFINITION OF DELAYED GASTRIC EMPTYING**

<table>
<thead>
<tr>
<th>DGE Grade</th>
<th>NGT Required</th>
<th>Unable to Tolerate Solid Oral Intake by POD</th>
<th>Vomiting/Gastric Distension</th>
<th>Use of Prokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4-7 days or reinsertion &gt; POD 3</td>
<td>7</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>B</td>
<td>8-14 days or reinsertion &gt; POD 7</td>
<td>14</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C</td>
<td>&gt;14 days or reinsertion &gt; POD 14</td>
<td>21</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

In contrast to pancreatic fistula, for which imaging is often not required, diagnosis of DGE frequently requires imaging. The most commonly used study is fluoroscopic upper gastrointestinal series. CT scan can also be used to visualize distended stomach and also rule out stenosis in the gastric outlet, which may require reoperation or endoscopic management.

**TREATMENT**

Grade A DGE is not commonly associated with vomiting. Prokinetic medications and TPN may not be required in the first 14 days after the operation. It only causes minor adjustment of the standard clinical pathway, and hospital discharge is often not delayed.

In contrast, grade B DGE involves significant adjustment of the standard clinical pathway. The patients often have vomiting if a nasogastric tube is not in place, necessitating replacement of this. TPN and prokinetic medications are frequently required. Hospital discharge is often delayed, as well patient recovery and likely the initiation of adjuvant therapy.

Grade C DGE necessitates major changes in clinical management and is often associated with other complications such as pancreatic fistula and intraabdominal abscess, which frequently requires radiological or even operative intervention. Prokinetic medications, nasogastric tube, and TPN are required. Hospital discharge and adjuvant therapy are frequently delayed. Table 76-4 shows parameters of DGE.
TABLE 76-4: PARAMETERS OF DGE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade A</th>
<th>Grade B</th>
<th>Grade C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical condition</td>
<td>Well</td>
<td>Often well/minor discomfort</td>
<td>Ill/bad/severe discomfort (increased overall risk owing to complications and procedures)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>No</td>
<td>Possibly yes (pancreatic leak or fistula, intraabdominal abscess)</td>
<td>Possibly yes (pancreatic leak or fistula, intraabdominal abscess)</td>
</tr>
<tr>
<td>Specific treatment</td>
<td>Possibly yes (prokinetic drugs)</td>
<td>Yes (prokinetic drugs, potential reinsertion of NGT)</td>
<td>Yes (prokinetic drugs, NGT)</td>
</tr>
<tr>
<td>Nutritional support</td>
<td>Possibly yes (slower return to solid food intake)</td>
<td>Yes (partial parenteral nutrition)</td>
<td>Yes (total parenteral or enteral nutrition via NGT, prolonged, ie, &gt;3 weeks postoperatively)</td>
</tr>
<tr>
<td>(enteral or parenteral)</td>
<td>No</td>
<td>Possibly yes (endoscopy, upper GI contrast study, CT)</td>
<td>Yes (endoscopy, upper GI contrast study, CT)</td>
</tr>
<tr>
<td>Diagnostic evaluation</td>
<td>No</td>
<td>No</td>
<td>Possibly yes (eg, abscess drainage, relaparotomy for complication, relaparotomy for DGE)</td>
</tr>
<tr>
<td>Interventional treatment</td>
<td>Possibly yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prolongation of hospital stay</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay of potential adjuvant therapy</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Post-Pancreatectomy Hemorrhage**

Perhaps the most severe complication of pancreatectomy, PPH only accounts for 1% to 8% of all complications after pancreatectomy. However, PPH results in an 11% to 38% overall mortality rate. In the early era of pancreatectomy, PPH was one of the major causes of postoperative death, partially due to the severity of bleeding, lack of intensive care units and interventional radiology, and the generally poor health status of the patients. Today PPH is rare in high-volume surgical centers. However, the importance of recognizing and treating PPH cannot be overemphasized.

**ETIOLOGY/RISK FACTORS**

Based on timing, PPH can be categorized as either early or late, according to the ISGPS definition (Table 76-5). Early PPH occurs within 24 hours postoperatively and is often a result of surgical error or patient coagulopathy. Late PPH occurs after 24 hours postoperatively and is often a sign of erosion of major blood vessels by the pancreatic juice. It is therefore common to find other complications such as pancreatic fistula or intraabdominal abscess along with late PPH. Another scenario of late PPH is pseudoaneurysm resulting from vascular injury during the index operation. PPH can occur in major visceral arteries or veins, pancreaticoenteric anastomosis, raw surface
of the pancreas after resection, and biliary stent placed intraoperatively. The common vascular source of PPH includes the stump of the gastroduodenal artery, splenic artery, branches of the superior mesenteric artery (eg, inferior pancreaticoduodenal artery), the splenic vein stump, or, rarely, an intrapancreatic artery (Wente et al., 2007b).

**TABLE 76-5: DIAGNOSTIC DEFINITION OF POST-PANCREATECTOMY HEMORRHAGE**
Proposed definition of postpancreatectomy hemorrhage (PPH)

Time of onset
- Early hemorrhage (≤24 h after the end of the index operation)
- Late hemorrhage (>24 h after the end of the index operation)

Location
- Intraluminal (intraenteric; eg, anastomotic suture line at stomach or duodenum, or pancreatic surface at anastomosis, stress ulcer, pseudoaneurysm)
- Extraluminal (extraenteric, bleeding into the abdominal cavity; eg, from arterial or venous vessels, diffuse bleeding from resection area, anastomosis suture lines, pseudoaneurysm)

Severity of Hemorrhage

Mild
- Small or medium volume blood loss (from drains, nasogastric tube, or on ultrasonography, decrease in hemoglobin concentration <3 g/dL)
- Mild clinical impairment of the patient, no therapeutic consequence, or at most the need for noninvasive treatment with volume resuscitation or blood transfusions (2-3 units packed cells within 24 h of end of operation or 1-3 units if later than 24 h after operation)
- No need for reoperation or interventional angiographic embolization; endoscopic treatment of anastomotic bleeding may occur provided the other conditions apply

Severe
- Large volume blood loss (drop of hemoglobin level by ≥3 g/dL)
- Clinically significant impairment (eg, tachycardia, hypotension, oliguria, hypovolemic shock), need for blood transfusion (>3 units packed cells)
- Need for invasive treatment (interventional angiographic embolization, or relaparotomy)

CLINICAL PRESENTATION

PPH can manifest itself in a variety of ways, such as bleeding from the nasogastric tube or surgical drains, hematemesis, melena, unexplained hypotension, tachycardia, etc. A small initial bleed from the nasogastric tube or surgical drain can be a sentinel bleeding, heralding a massive hemorrhage within a few hours. High clinical suspicion is therefore paramount in identifying and diagnosing PPH.

DIAGNOSIS

There has been a significant variety in the definition of PPH in the literature. In 2007, ISGPS released a consensus definition of PPH based on three criteria: (1) timing of onset: early (within 24 hours of the index operation), or late (after 24 hours since the index operation); (2) location: intraluminal (eg, pancreatic surface, anastomoses, gastric/duodenal ulcer/erosion, or hemobilia), or extraluminal (eg, arterial or venous vessel, operating field, external suture or staple line, or pseudoaneurysm); (3) severity of bleeding: mild or severe. Mild bleeding is characterized as a small or medium volume blood loss (drop of hemoglobin concentration of less than 3 g/dL) with no or minimal clinical impairment, no need for invasive intervention (reoperation or interventional angiography), and successful conservative treatment (fluid resuscitation and blood transfusion of 2 to 3 units packed red blood cells if it is an early bleed, or three units while hospitalized and late bleed). Severe bleeding is a larger-volume blood loss (decrease in hemoglobin concentration of ≥3 g/dL) and potentially life-threatening complications with tachycardia, hypotension, and/or oliguria; treatment involves the need for blood transfusion (≥3 units packed red blood cells) and/or invasive treatment (reoperation or interventional angiography).

Grade A PPH requires only a minor and temporary adjustment from the standard clinical pathway and has no major clinical impact. Hospital discharge is often not delayed. Grade B PPH, on the other hand, requires adjustment of a standard clinical pathway and often involves workup and intervention such as transfusion, radiological intervention such as embolization, reoperation, readmission, and/or intensive care unit transfer. Hospital discharge is often delayed. Grade C PPH is the most severe form and often requires immediate workup and interventions such as embolization.
or reoperation. Intensive care unit admission is frequent, and hospital stay is almost always prolonged.

**TREATMENT**

PPH is often a significant complication that requires prompt recognition and management. Once PPH is suspected, resuscitation is mandatory, while diagnostic testing may be carried out at the same time to identify the location and cause of the bleed. The diagnostic tests include, but are not limited to, complete blood count, coagulation panel, CT angiography, etc. Transfusion may be required for grade B PPH and is often necessary for grade C PPH. For pseudoaneurysm, radiological embolization is frequently used. If the PPH is caused by disruption of the anastomosis or erosion of the visceral vessels by the pancreatic juice, reoperation is frequently necessary.

**Biliary Leak**

Biliary leak is a fairly uncommon complication following pancreaticoduodenectomy. This is perhaps due to the resection of the distal, also the narrowest, portion of the common bile duct, and the common use of larger-caliber anastomosis from hepatojejunostomy. Miedema et al. (1992) reported 24 patients with postoperative biliary-enteric anastomotic leak rate out of 279 patients (9%) who underwent pancreaticoduodenectomy at the Mayo Clinic from 1980 to 1989. Sohn et al. (2003) further reported that of 1061 patients who underwent pancreaticoduodenectomy at Johns Hopkins Hospital from 1995 to 2000, only 39 (3.7%) required postoperative drainage for biliary leaks from etiologies such as from biliary anastomotic disruption, undrained biliary segments, or T-tube/bile stent dislodgment. Of note, out of 1061 patients, 342 had preoperative biliary drainage, which may have decreased the incidence of postoperative biliary leak. In a report by Behrman et al. (2004) from the University of Tennessee, no biliary complication was reported out of 125 patients who underwent pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy.

Nevertheless, biliary leak increases postoperative morbidity and mortality. In Miedema’s report, mortality increased from 2% to 17% with biliary leak (p <0.05).
ETIOLOGY/RISK FACTORS

No particular risk factors have been identified. In the report by Miedema et al. (1992), biliary leak is not associated with bile duct size, preoperative or postoperative bile duct drainage, or preoperative serum bilirubin level.

DIAGNOSIS

Biliary leak usually does not require special diagnostic workup. It is often evidenced by bile in the fluid collected by the surgical drain left at the time of operation. If it presents as abdominal abscess, CT scan can often be sufficient.

TREATMENT

Although postoperative biliary leak is associated with increased morbidity and mortality, it usually can be managed conservatively without percutaneous drainage or reoperation. For some patients with high-volume output, diversion with a transhepatic catheter may be helpful. Miedema et al. (1992) only reported 3 out of 24 patients who required reoperation. In Sohn et al.’s report, only 3.7% required percutaneous drainage.

Pancreatic Insufficiency

Pancreatic exocrine insufficiency is fairly common with chronic pancreatitis or pancreatic cancer even prior to pancreatectomy. In a recent systematic review, Tseng et al. (2016) found that 20% to 63% of patients presented with preoperative pancreatic exocrine insufficiency. This rate increased to 67% to 80% 6 months after pancreatectomy. Another recent meta-analysis has found that exocrine insufficiency has occurred in 27% patients after pancreatectomy, with pancreaticoduodenectomy and female gender as independent risk factors (Kachare et al., 2014). The extent of pancreatic resection directly predicts the probability of developing pancreatic exocrine insufficiency imposing a significant negative impact on the quality of life (Okano et al., 2016). However, the mechanism of pancreatic exocrine insufficiency is multifactorial (Phillips, 2015). For example, the resection of stomach and duodenum can change the gut pH and interferes with the
pancreatic enzymatic activities (Tran et al., 2009). Pancreaticojejunostomy and hepatojejunostomy can cause asynchrony between pancreatic enzyme delivery and food absorption (Bruno et al., 1995; Sikkens et al., 2014).

Pancreatic exocrine insufficiency is often diagnosed with a combination of clinical presentation and pancreatic exocrine function tests with fecal fat content and fecal elastase determination. Patients may present with malnutrition. Steatorrhea is often a late symptom of pancreatic exocrine insufficiency and patients often avoid fatty food, further delaying the onset of steatorrhea.

Currently the mainstay therapy is pancreatic enzyme supplementation or replacement. Pancrelipase, often in the delayed-release form (Creon), is often used. A recent study by Whitcomb (2016) has shown that pancrelipase significantly increases fat and nitrogen absorption. Proton-pump inhibitors (PPIs) are also often used to suppress gastric pH, given the decrease pancreatic bicarbonate secretion. However, no significant difference in fat absorption has been found in the PPI group and the placebo group (Sander-Struckmeier et al., 2013).

**New-Onset Diabetes**

Since pancreatectomy removes pancreatic endocrine components, it is not uncommon for patients to develop new-onset insulin-dependent diabetes. A study comparing quality of life after total pancreatectomy and partial pancreatic resection found that postoperative diabetes after both procedures had the largest negative impact on leisure and physical activities (Epelboym et al., 2014; Petrin et al., 1995).

If the pancreatectomy is for chronic pancreatitis, the pancreas is likely already compromised before the surgery. It is therefore not surprising that chronic pancreatitis patients have an even higher risk of insulin-dependent diabetes than other pancreatic surgical patients (Cannon et al., 2012; Maeda and Hanazaki, 2011). A large systematic review has shown that the risk of new-onset diabetes after distal pancreatectomy in patients with chronic pancreatitis is 39%, and the risk of development of diabetes after resection of pancreatic tumor is only 14% (De Bruijn and van Eijck, 2015). The amount of resection is also positively correlated with the risk of diabetes (Parikh and Lillemoe, 2015). On average, 77% of the patients with new-onset diabetes will require insulin (De Bruijn and van Eijck, 2015).
In patients with new-onset diabetes after pancreatectomy, glucose control is more difficult due to severe fluctuations in glucose levels associated with exogenous insulin and deficiency of pancreatic polypeptide (Cui and Andersen, 2011; Seymour et al., 1988). Mortality from hypoglycemia has been reported in patients with pancreaticoduodenectomy, and it was thought to result from a combination of exogenous insulin and lack of glucagon (Gall et al., 1981). Patients with distal pancreatectomy are at particularly high risk for hypoglycemia, because the glucagon-producing alpha cells are located mainly in the pancreatic body and tail (De Bruijn and van Eijck, 2015).

**SUMMARY**

The development and optimization of different types of pancreatectomy have occurred because of a deepening understanding of the associated pathophysiology, advancement in surgical methods, diagnostic tools, and perioperative management, and also management of complications. The mortality associated with pancreatectomy has decreased significantly over the years, from a dismal 40% to less than 2% in high-volume centers. The emergence of high-volume centers have been one of the most important factors in the reduction of mortality. Although still a major undertaking, pancreatectomy nowadays is no longer associated with dreadful outcomes that some in the medical community and the general public still believe exist.

Postoperative morbidity, however, remains common, with a rate between 20% to 45% in most reports. Although most complications can be managed conservatively and will resolve within a few weeks, these complications delay patient recovery and the initiation of adjuvant therapy. Some complications such as hemorrhage can also be life-threatening. These complications underscore the importance of vigilant postoperative management, and also indicate the limitation of our understanding of the pathophysiology of the pancreas.

**FURTHER READING**


Lowy AM, Leach SD, Philip PA. *Pancreatic Cancer.* Springer Science; 2008.


SPLEEN AND ADRENAL
BACKGROUND

The spleen was regarded by Galen as “an organ of mystery,” by Aristotle as unnecessary, and by Pliny as an organ that might hinder the speed of runners.¹ In many societies, the spleen was also thought to be affiliated with mood. The word spleen comes from a Greek word that has idiomatic equivalent of the heart in English, that is, to be good-spleened means to be good-hearted or compassionate. In contrast, the spleen has also been associated with melancholy, and in 19th-century England, women in bad humor were said to be afflicted by the spleen or the vapors of the spleen.

Until relatively recently, the spleen was considered expendable. The gradual realization of the valuable role of the spleen in host defense, beginning with reports of fulminant sepsis in children after splenectomy for hematologic disease, has increased interest in splenic conservation techniques.²³ The indications for splenectomy in both the emergency and elective settings continue to evolve. The introduction of laparoscopic approaches has decreased the morbidity of surgery, but a balance between the indications for splenectomy and the long-term consequences of splenectomy,
particularly sepsis, must always be considered.

In this chapter, we review the anatomy, physiology, and pathology of splenic diseases, before addressing operative techniques and strategies, focusing on the laparoscopic approach.

**RELEVANT ANATOMY**

**Gross Anatomy**

The spleen arises by mesenchymal differentiation along the left side of the dorsal mesogastrium in juxtaposition to the anlage of the left gonad in the 8-mm embryo. The organ ultimately migrates to the left upper quadrant.

In the healthy adult, the spleen weighs 150 g (range, 75-250 g), although there are variations based on sex, age, and racial background. Although the ultrasonographic upper limit of normal for spleen size is 12 cm, it is larger in men and taller or heavier people, and sex- and size-corrected normal values are available. The spleen is not normally palpable in adults. When the spleen tip can be felt below the left costal margin, splenomegaly should be assumed and further investigated.

The spleen resides in the posterior portion of the left upper quadrant lying deep to the 9th, 10th, and 11th ribs, with its long axis corresponding to that of the 10th rib. Its convex superior and lateral surfaces are immediately adjacent to the undersurface of the left leaf of the diaphragm. The configuration of the concave medial surface of the spleen is a consequence of impressions made by the stomach, pancreas, kidneys, and splenic flexure of the colon (Fig. 77-1).
FIGURE 77-1 Gross anatomy of the spleen.

The position of the spleen is maintained by several suspensory ligaments, which need to be divided during a splenectomy to allow full mobilization of the organ. These are the gastrosplenic, splenophrenic, splenocolic, and splenorenal ligaments (Figs 77-2 and 77-3). The gastrosplenic ligament contains the short gastric vessels that course to the splenic hilum from the greater curvature, whereas the splenorenal ligament contains the pancreas and the splenic vessels. The remaining ligaments are generally avascular, except in patients with portal hypertension or myeloproliferative disorders. The tail of the pancreas is in direct contact with the spleen in 30% of cases and within 1 cm of the spleen in three-quarters of patients.\(^6\)
FIGURE 77-2 Anatomy of the spleen showing complicated peritoneal reflections in the region of the hilus.
Accessory spleens, which are distinct and separate masses of splenic tissue, have been reported in 14% to 30% of patients undergoing splenectomy, with a higher incidence in patients with hematologic disorders and a lower incidence at autopsy in people without hematologic or splenic disease (7%). They are present in decreasing order of frequency in the hilum of the spleen, tail of the pancreas, greater omentum, gastroplenic ligament, and splenocolic ligament (Fig. 77-4A). Accessory spleens may also occur in the pelvis, either in the presacral region or adjacent to the left ovary in the female, and in the scrotum in juxtaposition to the left testicle in the male (Fig. 77-4B). The accessory spleens can vary in size and may be small lesions that can be easily missed unless a careful examination is performed (Fig. 77-5).
The accuracy for intraoperative localization of accessory spleens seems higher than computed tomography (CT) scan, and so routine preoperative imaging for the purpose of diagnosis of accessory spleens prior to splenectomy is not routinely recommended.\(^8\)

**FIGURE 77-4** A. The more common locations of accessory spleens. Accessory spleens are also found in the left ovary, in the left testicle along the course of the left ureter, and in the lesser sac and greater omentum. B. Locations of accessory spleens. Note position of presacral and paraureteric splenuli.
Splenic Blood Supply

The spleen is supplied by the splenic artery, the short gastric vessels, and the left gastroepiploic artery. The splenic artery commonly arises from the celiac axis and is the longest of its 3 branches. Most of the splenic arterial supply is derived through this vessel. The 3 to 5 short gastric vessels lie in the gastrospenic ligament, and there is often a connection between some of the short gastrics and the superior polar branch of the splenic artery. Similarly, there is often a connection between the left gastroepiploic and the inferior polar branch of the splenic artery. The splenic artery has a very tortuous course and has a highly variable pattern of distribution. In 1942, Michels divided the splenic arterial supply into 2 types: distributed and magistral.
• **Distributed type**: The most common variation seen in 70% of cases. Here the main splenic artery is short, dividing into many long branches (6-12) that originate between 3 and 13 cm from the hilum and enter the spleen on the medial aspect, involving 75% of the medial surface (Fig. 77-6A).

**FIGURE 77-6** Different types of splenic artery distribution. The terminal vessels divide the spleen into independent lobes or segments **A**. Distributed type: short splenic artery that divides into long branches that enter the spleen medially, involving 75% of the medial surface. **B**. Magistral (bundled) type: the splenic artery is long with fewer hilar branches. (Reproduced with permission from Souba WW, Fink MP, Jurkovich GJ, et al: *ACS Surgery: Principles and Practice*, 6th ed. Hamilton, ONT, Canada: BC Decker; 2007.)
• **Magistral or bundled type:** The less common variation seen in 30% of cases. Here a long main trunk divides near the hilum into 3 to 4 large branches that enter the spleen medially but only involve 30% of the spleen’s medial surface (Fig. 77-6B).

The common splenic artery divides into 2 lobar arteries (superior and inferior) in 86% of cases and 3 lobar arteries in 12% of cases (superior, inferior, and accessory). Each lobar artery divides into segmental arteries with a total of 3 to 5 segmental arteries in 94% of cases. These segmental arteries supply blood to a corresponding wedge-shaped splenic segment. There is a relatively avascular plane between the lobes and segments, so resection of the segmentally devascularized spleen can be performed without significant blood loss. Understanding these relationships is important in performing partial splenectomy.10

The splenic artery also has a pancreatic branch (pancreatica magna) that is worthy of note. Occlusion of this branch, most often seen after proximal splenic artery embolization, can lead to pancreatitis.

The major venous drainage flows through the splenic vein, which usually receives the inferior mesenteric vein centrally and then joins the superior mesenteric vein to form the portal vein. The veins generally lie behind the arteries except in the hilum where the anatomy is variable.

**Histology**

The spleen is made up of a capsule that is normally 1 to 2 mm thick and trabeculae that surround and invaginate the pulp. Approximately 25% of the parenchyma (Fig. 77-7) is made up of “white pulp” that functions as an immunologic organ, with the remaining 75% made up of the “red pulp” that phagocytizes particulate matter from the blood. The 2 zones are separated by a narrow marginal zone.
Fast (closed) circulation—In this type of splenic circulation, blood flows directly from the arterioles to venules.

Slow (open) circulation—In this type of splenic circulation, the blood passes through the red pulp.
FIGURE 77-7 Diagram illustrating splenic compartments and the 2 different types of circulation.

The white pulp, which is central and surrounds a central artery, is made of lymphatic nodules with germinal centers and periarterial lymphatic sheaths that constitute a reticular network filled with lymphocytes and macrophages. Peripheral to the white pulp is the marginal zone that contains end arteries arising from the central artery and from peripheral penicillary arteries. The marginal zone contains lymphocytes and macrophages and red blood cells (RBCs) that have exited from terminal arteries. The marginal zone also contains the marginal sinus, which filters material from the centrally located white pulp. Locally produced immunoglobulins enter the marginal zone, eventually coursing to the bloodstream.

Physiology

The spleen receives 250 to 300 mL of blood per minute, which corresponds to 5% of the cardiac output. At any given time, however, it contains only 30 to 40 mL of blood. Although the spleen is not necessary for human life, it performs important functions that are generally attributed to its unique blood flow pattern. As the blood enters the spleen, it can take 2 paths of flow: a fast (closed) circulation that takes the blood directly from the arterioles to the venules or a slower (open) circulation that takes the blood through the pulp. The majority (90%) of flow is of the slow (open) type, which exposes the circulating cells and erythrocytes to splenic macrophages in the red pulp (see Fig. 77-7).

Functions of the spleen can be divided into the following:

*Erythrocyte quality control and removal of defective red cells:* This is achieved through pitting and culling. *Pitting* refers to the removal of rigid structures such as Heinz bodies (denatured intracellular hemoglobin), Howell-Jolly bodies, and hemosiderin granules from red cells. The process involves the removal of nondeformable intracellular substances from deformable cells. The rigid body is phagocytized, while the deformable cytoplasmic mass passes into the sinus and returns to the general circulation. The postsplenectomy blood smear is thus characterized by the presence of circulating erythrocytes with Howell-Jolly and Pappenheimer
bodies (siderotic granules).

*Culling* is the term applied to the spleen’s ability to remove red cells that are aged or abnormal. During its 120-day life cycle, the red cell spends an estimated minimum of 2 days within the spleen. Normally, as the red cell ages after a life span of approximately 120 days, it loses osmotic balance and membrane integrity and therefore deformability. When these cells lose their deformability, they are phagocytized by native macrophages. The spleen does not represent the only site for red cell destruction, and there is no difference in red cell survival after splenectomy. About 20 mL of RBCs are removed daily from the blood.

*Pooling:* In health, the spleen does not serve as an important reservoir for blood cells but does so for platelets. Normally, about one-third of the platelet mass is pooled in the spleen, and this pool exchanges freely with the circulating platelets that have a life span of about 10 days. With splenomegaly, a large proportion of platelets are sequestered in the spleen (up to 80%), and this, coupled with accelerated platelet destruction in the spleen, accounts for thrombocytopenia. The role of the spleen in platelet storage also explains the elevation in platelet count that is seen after splenectomy.

The neutrophil has a half-life of about 6 hours; hence, 85% of neutrophils either migrate at random into tissues or are destroyed within 24 hours. Although the role of the spleen in the destruction of neutrophils under normal conditions is not well quantified, this role is amplified in some hypersplenic states, with resulting neutropenia. This augmented removal can occur because of splenic enlargement and accelerated sequestration of granulocytes or because of enhanced splenic removal of altered granulocytes, as seen in immune neutropenias.

*Hematopoiesis:* The spleen has an important hematopoietic function in fetal life that ceases by the seventh intrauterine month and does not occur in healthy adults with exception in certain pathologic conditions where bone marrow is unable to meet the needs (ie, extramedullary hematopoiesis).

*Filtration:* Macrophages residing in the splenic parenchyma capture cellular and noncellular material from blood, including encapsulated bacteria such as pneumococci, and destroy them. This function explains the increased risk of infections caused by encapsulated organisms that is
seen after splenectomy.

*Antibody synthesis in the white pulp*: In addition to the phagocytosis of antibody-coated cells, the immunologic functions of the spleen include antibody synthesis (especially immunoglobulin M [IgM]); generation of lymphocytes; and production of tuftsin, opsonins, properdin, and interferon. Foreign antigens that are filtered in the white pulp are presented to lymphoid cells. Here the immunoglobulin response is mounted, leading to release of antibodies.

**SPLENIC TRAUMA AND RUPTURE**

**Etiology**

Splenic rupture is defined as any disruption of the splenic parenchyma or capsule. It can be spontaneous, iatrogenic, or traumatic.

Spontaneous splenic rupture is a rare surgical emergency usually caused by splenic infiltration by hematologic, neoplastic, or infectious diseases. In a review of over 800 cases of spontaneous rupture, 6 major etiologic groups were defined: neoplastic (30.3%), infectious (27.3%), inflammatory (20.0%), drug and treatment related (9.2%), mechanical (6.8%), and normal spleen (6.4%). The majority of patients were treated with splenectomy with an overall mortality rate of 12%.11

Iatrogenic splenic injuries during abdominal procedures, especially colectomy, are well documented (Fig. 77-8). In a 16-year review of nearly 14,000 colectomies performed at the Mayo Clinic, splenic injury requiring a splenectomy or repair occurred in 0.4%. Although repair was attempted in 50% of cases, the majority of these patients ultimately required splenectomy. Those with an incidental splenectomy had high 30-day morbidity (34%) and mortality (15%).12 A review of the national inpatient sample database focusing on colorectal surgery between 2006 and 2008 reported a higher incidence of splenic injury of 1%, with 85% of patients treated with splenectomy.13 Patients who undergo an incidental splenectomy during colorectal surgery for cancer have a poorer prognosis compared to the nonsplenectomized group, suggesting a negative long-term impact of splenic injury in these patients.14
FIGURE 77-8 A large splenic hematoma that developed after intraoperative injury to the spleen during gastric bypass surgery. The patient was hemodynamically stable, and the hematoma resolved without any further intervention.

Colonoscopy has also been associated with splenic injury. Although the rate is extremely low at 0.001%, it is associated with significant morbidity, with more than 70% of patients requiring an operative intervention, and 5% mortality.

The most common cause of splenic rupture is traumatic injury. Mechanism of injury can be blunt or penetrating. The trajectory of the penetrating wound may pass through the anterior abdominal wall, the posterior abdominal wall, the flank, or transthoracically, piercing the pleural space and diaphragm. It can be either isolated to the spleen or associated with injuries to surrounding structures including the stomach, left kidney, left
Diagnostic Studies

Signs associated with bleeding might be seen on investigation. A complete blood count might show a decrease in hemoglobin or hematocrit or an increase in white blood cell (WBC) count. A blood gas obtained in the trauma bay might show an increased lactate or abnormal base excess depending on how severe the bleeding is and how long the patient has been bleeding. Findings on routine abdominal films such as fractured ribs, elevated left hemidiaphragm, enlarged splenic shadow, medial gastric displacement, and widening of the space between the splenic flexure and the preperitoneal fat pad may be helpful. A focused assessment with sonography for trauma (FAST) examination may show evidence of intra-abdominal fluid accumulation. However, all these findings are not specific and can be found in trauma patients with no splenic injuries. Intravenous contrast-enhanced CT scan is the gold standard diagnostic study that will also provide detailed information regarding the American Association for the Surgery of Trauma (AAST) grading for severity of injury\(^{17}\) (Table 77-1).

**TABLE 77-1: AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA SPLEEN INJURY SCALE**
Management

The first total splenectomy for trauma was performed by Nicolaus Matthias in 1678 in Cape Town, South Africa, on a patient whose spleen protruded through a flank wound. However, partial splenectomy for trauma antedated this procedure, with the first successful partial splenectomy for trauma reported by Franciscus Rosetti in 1590. Increasing understanding of the functions of the spleen and increased risk of infection in splenectomized patients have rejuvenated interest in splenic salvage in trauma. The first successful partial splenectomy for trauma in modern times was reported by Campos Christo in 1962.¹

<table>
<thead>
<tr>
<th>Grade&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Injury Type</th>
<th>Description of Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma</td>
<td>Subcapsular, &lt;10% surface area</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>Capsular tear, &lt;1 cm parenchymal depth</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma</td>
<td>Subcapsular, 10%-50% surface area</td>
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<tr>
<td></td>
<td></td>
<td>Intraparenchymal, &lt;5 cm in diameter</td>
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<tr>
<td></td>
<td>Laceration</td>
<td>Capsular tear, 1-3 cm parenchymal depth that does not involve a trabecular vessel</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma</td>
<td>Subcapsular, &gt;50% surface area or expanding; ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma ≥5 cm or expanding</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>&gt;3 cm parenchymal depth or involving trabecular vessels</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Laceration involving segmental or hilar vessels producing major devascularization (&gt;25% of spleen)</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Completely shattered spleen</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Hilar vascular injury with devascularizes spleen</td>
</tr>
</tbody>
</table>

<sup>a</sup>Advance 1 grade for multiple injuries up to grade III.

The observation that splenic injury may heal itself has also supported nonoperative management (NOM) of splenic injuries. While this practice was largely accepted in the treatment of injured pediatric patients to salvage the spleen and its immunologic function, NOM is also the treatment of choice for hemodynamically stable adults with blunt splenic injuries, regardless of injury severity (Fig. 77-9). Penetrating injuries, hemodynamic instability, and associated peritonitis are all treated with laparotomy, as per the 2012 Eastern Association for the Surgery of Trauma (EAST) guidelines.18
FIGURE 77-9  Suggested management algorithm for splenic trauma. CT, computed tomography.

NOM of blunt spleen injury requires a multidisciplinary strategy including careful clinical monitoring, repeated laboratory testing, and radiologic investigations. NOM should only be carried out in an institution that has a monitored intensive care unit, available surgical expertise, and easy access to the operating room. NOM procedures include supportive medical
management and angioembolization. The success rate depends on severity of injury and is reported greater than 95% for grade I injuries, greater than 90% for grade II injuries, and greater than 80% for grade III injuries. Splenic salvage is much less likely with grade IV and V injuries. In a multicenter review of 338 patients with grade IV or V blunt splenic injuries, 40% of patients were operated on immediately, while the remainder had an attempt at NOM. The success rate for NOM in these selected patients was 66% for grade IV and 40% for grade V injuries. Thus, overall, nearly two-thirds of patients with grade IV or V injuries required surgery, and there was higher mortality in patients who failed NOM compared to those in whom it was successful. Prognostic factors that predict failure of NOM of blunt splenic trauma were evaluated in a systematic review. The strongest predictors were age >40, Injury Severity Score >24, and grade III to V injury, with moderate evidence for presence of contrast extravasation or “blush” on CT scan.

Splenic artery embolization (SAE) is an important adjunct for NOM, but its precise role remains controversial. A meta-analysis to evaluate NOM of blunt splenic injury found that the overall failure rate was 8.4% (95% confidence interval [CI], 6.7%-10.2%) with failure rates increasing with more severe injuries, from about 5% in grade I to 83% in grade V. The addition of SAE was associated with higher splenic salvage rates for more severe injuries compared to observational management alone (56% vs 83% for grade IV and 17% vs 75% for grade V). Most studies have suggested that splenic function is preserved after SAE, but multiple different parameters were used. There are no reported cases of overwhelming postsplenectomy infections after SAE, and routine vaccination is not used. Splenic embolization, however, has its own risks and may be complicated by splenic abscess, infarction, pain, fever, coil migration, pleural effusion, contrast nephropathy, and bleeding. Currently, angiography is recommended for hemodynamically stable patients with grade III to V injuries, contrast blush, moderate hemoperitoneum, or clinical evidence of ongoing bleeding.

NOM of splenic injuries should not exceed 24 hours. Failure of NOM is defined as persistent bleeding evident by laboratory testing, hemodynamic changes, or persistent requirement of blood transfusion after 24 hours. Failure of NOM is treated by laparotomy and splenectomy or splenorrhaphy.

After discharge, there is a lack of consensus on restriction of activities,
with most restricting activity for >2 months for high-grade injuries managed nonoperatively. Patients should be aware of the risk of delayed splenic rupture, with the 180-day risk of readmission for splenectomy of 1.4% in one population-based study.

**LOCAL SPLENIC DISORDERS**

**Splenic Artery Aneurysm**

Splenic artery aneurysm was first described by Baussier in 1770, and St. Leger Brockman described one of the first surgical cases in 1930. Although mycotic aneurysm can be seen in the splenic artery, the majority are idiopathic. The splenic artery is the most common visceral artery aneurysm and the third most common site of intra-abdominal aneurysms, after aneurysms of the abdominal aorta and iliac arteries. The incidence in autopsy series ranges between 0.02% and 0.16%, with a female predominance (4:1). They are commonly associated with pregnancy and portal hypertension. The incidence of splenic aneurysm is much higher in patients with cirrhosis and portal hypertension. Splenic artery aneurysms have been reported in 14% of patients awaiting liver transplant, which can lead to major hemorrhage after transplant. Splenic artery aneurysms are also seen at a higher incidence in patients with arteritis, arterial fibrodysplasia, collagen vascular disease, and α1-antitrypsin deficiency. Most are true aneurysms, but pseudoaneurysms may also develop as complications of pancreatitis and trauma.

In a contemporary review of 217 splenic aneurysms seen at the Mayo Clinic, the mean age at presentation was 62 years, with 79% of patients being female. Over 90% of the patients were asymptomatic, with a mean aneurysm size of 3.1 cm. Although more than 10% of men presented with a rupture, this rate was less than 3% in women, in large part due to larger aneurysm sizes in men. The mean size for nonruptured cases was 2.2 cm, and the smallest-diameter aneurysm to rupture was 2.2 cm.

Splenic artery aneurysms are often incidental findings in asymptomatic patients. Most are under 2 cm in size, but on occasion, they can be much larger. They are generally saccular and solitary, and occur at a bifurcation in the splenic hilum. Peripheral calcification and mural thrombus are
frequently noted (Fig. 77-10). Patients may present with symptoms of left upper quadrant or epigastric pain radiating to the shoulder. The overall risk of rupture is less than 2% but is higher for aneurysms larger than 2 cm, in liver transplant patients, and in pregnancy. Such ruptures have been associated with maternal and fetal death rates of 22% and 15%, respectively. Ruptures occur in the third trimester of pregnancy in 69% of cases.

**FIGURE 77-10** A CT scan of a large splenic artery aneurysm with calcified wall. This calcified wall can also be seen on plain abdominal roentgenogram.

Rupture of the aneurysm is manifested by sudden abdominal pain. If the rupture is initially contained in the lesser sac, the patient may have upper abdominal pain but be hemodynamically stable. Once the rupture overflows into the peritoneal cavity, diffuse pain and hemorrhagic shock ensue. This sequence of events is termed the “double rupture phenomenon.” Mortality after emergency surgery is as high as 40%.

Surgical resection in all symptomatic aneurysms is recommended; however, criteria for elective repair of asymptomatic aneurysms are not firm. In general, the presence of an aneurysm larger than 2 cm is an indication for surgery if the patient is a reasonable operative risk. Asymptomatic patients with aneurysms between 1 and 2 cm should be closely monitored with serial
imaging done initially every 6 months. Aneurysms of any size detected in pregnancy should be treated because many of the ruptured aneurysms during pregnancy are less than 2 cm in size. This should be done before the third trimester, when the risk of rupture is at its peak. Liver transplant patients have a higher incidence of aneurysms and a higher risk of rupture, including in the posttransplant period, with a mortality over 50%. This has led to recommendations to treat splenic artery aneurysms over 1.5 cm in size with embolization prior to liver transplantation.

The traditional approach to repair for lesions in the proximal or middle of the artery includes resection and primary end-to-end anastomosis, or proximal and distal ligation with resection of the involved segment. Proximal ligation is reasonable because the spleen will not become ischemic following central ligation of the main splenic artery. Distal lesions located close to the hilum generally require splenectomy with resection of the involved splenic artery, now generally done laparoscopically (Fig. 77-11). The overall mortality rate ranges from 1% to 3%, with a perioperative complication rate of 9% to 25% due to splenic or pancreatic injury.

FIGURE 77-11 A 3-dimensional CT reconstruction of a partially thrombosed large splenic artery aneurysm with a smaller aneurysm more distal. Both aneurysms were treated by a laparoscopic splenectomy.

Percutaneous transcatheter embolization techniques have been increasingly used and are preferred over surgery for most splenic artery
aneurysms if the anatomy is suitable. The endovascular therapeutic options include stenting, coil embolization, and the use of glue, N-butyl-2-cyanoacrylate; their uses vary based on aneurysm size and location, and there is not enough evidence to support the use of one over another. These techniques have been increasingly used since 2000, and a systematic review reports a technical success rate of over 95%. Complications of endovascular repair include treatment failures, postprocedural pain, and abscess formation, as well as pancreatitis due to occlusion of the pancreatica magna vessel. Major postoperative complications are higher in the open repair (1.1%) versus endovascular patients (0.8%). In the long term, however, there are more late complications in the endovascular group with a greater need for subsequent interventions compared to open repair (3.2% vs 0.5% per year). Follow-up after endovascular repair is mandatory. Decision analysis modeling suggests that the endovascular approach is less costly and more effective than open surgery. The endovascular approach has also been used in the emergency setting to treat ruptured aneurysms.

**Cysts**

Splenic cysts are classified as primary or secondary (pseudocysts). Some splenic tumors may also have a cystic component (Fig. 77-12). Primary cysts have an epithelial lining and can be nonparasitic or parasitic (echinococcal).
PARASITIC PRIMARY CYSTS

Worldwide, *Echinococcus* infection (hydatid disease) is the most common cause of a splenic cyst. The spleen is the third most common site of disease, after the liver and lung. *Echinococcus granulosus*, the most commonly implicated species, usually results in a unilocular cyst composed of an inner germinal layer (endocyst) and an outer laminated layer (ectocyst) surrounded by a fibrous capsule. Unlike the nonparasitic cysts, these are filled with fluid under positive pressure and also contain daughter cysts and infective scolices. Echinococcal cysts are usually asymptomatic unless they reach a size causing pressure symptoms or become secondarily infected or rupture. Overall, splenic involvement is rare, even in endemic areas, and comprises only 0.5% to 4% of all hydatid disease.40 Once splenic disease is found, concomitant disease is usually found in other organs, with the liver and peritoneum the most common locations.

Splenic hydatid cysts grow slowly, approximately 0.3 to 2.0 cm per year,41 and most patients remain asymptomatic for a long time. Symptoms occur due to the mass effect on nearby organs, usually with nonspecific and/or left upper quadrant abdominal pain. Diagnosis is made using imaging tests including ultrasound, CT, and magnetic resonance imaging (MRI) studies that demonstrate a septated cystic mass that contains daughter cysts. For diagnostic purposes, the older Casoni skin test has been replaced with serologic testing. Multiple serologic tests are available and include immunophoresis, enzyme-linked immunosorbent assay (ELISA), and latex and indirect hemagglutination. Sensitivity rates of 85% to 90% are seen with both ELISA and indirect hemagglutination testing; overall, ELISA testing is thought to be optimal. These are used for screening and diagnosis and can also be used on follow-up to detect any recurrences.40,41

Recommended management of splenic hydatid cysts is based on size and concomitant disease; options include medical management, percutaneous techniques (puncture, aspiration, injection, reaspiration [PAIR]), and surgical intervention. Medical management with anthelmintics (eg, albendazole, mebendazole, praziquantel) as a sole treatment modality is controversial
given low absorption of orally administered medication and subtherapeutic concentration in the cyst. Some still advocate for small cysts being treated with anthelmintic drugs alone. The PAIR technique is used in conjunction with anthelmintic therapy in patients with prohibitive surgical risks or who refuse surgery and is safe for cysts under 5 cm in diameter. Larger and/or symptomatic cysts are treated surgically due to the risk of rupture. Traditionally, a complete splenectomy is advocated to reduce the risk of recurrence and is the treatment of choice. This is especially true for multiple or centrally located cysts or in patients with concomitant abdominal disease elsewhere. Care should be taken to avoid spilling the contents of the cyst. Intraoperatively, the lesions can be sterilized by instilling a 3% sodium chloride solution into the cysts. If intraperitoneal spillage occurs during the dissection, anaphylactic hypotension may occur and require epinephrine. With newer techniques emerging and concern for postsplenectomy septic complications, splenic-preserving procedures are being considered for small or peripherally located cysts. These include partial splenectomy, cyst enucleation, deroofing with omentoplasty, and internal drainage with cystojejunal anastomosis. Small case series show no recurrence after spleen-preserving procedures for small peripheral cysts in young patients.

Other studies comparing outcomes after total splenectomy and spleen-preserving surgery have found no difference in recurrence; however, these are all retrospective and heterogeneous studies, and definitive recommendations cannot be made. Larger studies are yet to be done, and the role of splenic-preserving procedures for hydatid cysts is not well established. The use of laparoscopy has also not been widely accepted in treating hydatid cysts because of a fear of spillage and anaphylaxis.

NONPARASITIC PRIMARY CYSTS

Nonparasitic primary cysts are increasingly discovered incidentally on imaging done for a variety of reasons. According to Morgenstern’s classification, nonparasitic splenic cysts are classified based on pathogenesis as congenital, neoplastic, traumatic, or degenerative (Table 77-2).

| TABLE 77-2: CLASSIFICATION OF NONPARASITIC SPLENIC CYSTS |
Cysts with mesothelial, transitional, or epidermoid epithelial cell lining

With characteristic gross appearance (interior trabeculation), despite lack of cellular lining

Neoplastic

Neoplasms of endothelial origin

Lymphangioma

Hemangioma

Cystified primary or metastatic tumors

Traumatic

Cysts in which there is clear evidence of normal splenic architecture, followed by cyst appearance after documented trauma; usually from nonresolving subcapsular hematoma

Degenerative

Cystified splenic infarcts


Cysts with mesothelial, epidermoid, or transitional epithelial linings are probably congenital in origin, originating from an infolding of peritoneal mesothelioma during splenic development. The cellular lining can desquamate and be absent in places, but these cysts have a characteristic gross appearance, with a white, glistening interior containing coarse fibrous trabeculations. The cyst fluid can be clear or cloudy and ranges in color from almost clear to yellow, green, or brown. The fluid may show elevated levels of carcinoembryonic antigen (CEA) and CA 19-9. A calcified portion of the cyst wall may also observed in a small proportion of these cysts.

Congenital cysts of the spleen occur in children and in young adults in 75% of cases. About two-thirds of the patients are female. The clinical manifestations are dependent on the size and can include left upper abdominal discomfort, pain, or fullness. True dermoid cysts of the spleen are exceedingly rare; less than 10 cases have met the pathologic criteria of a squamous epithelium with dermal appendages such as hair follicles and sweat glands.

It can be difficult to differentiate these cysts from one another based on
imaging only, and usually the diagnosis is made when symptomatic cysts, usually greater than 5 cm, are excised and analyzed histologically.\textsuperscript{44} Asymptomatic cysts, which are often smaller, are observed with no need for surgical resection. The recommendation for resection of splenic cysts over 5 cm originated in 1992 based on a report by Musy et al.\textsuperscript{45} and was reinforced in subsequent literature.\textsuperscript{43} Some sources cite the 25\% spontaneous rupture risk for cysts larger than 5 cm with an associated high mortality rate, but this was in the context of hemangiomas. More recent work by Kenney et al.\textsuperscript{46} reviewed 115 patients with splenic cysts, including 16 with cysts larger than 5 cm. There was only 1 patient with a large cyst who presented with rupture after a fall. The authors concluded that size should not be used to determine the need for intervention.\textsuperscript{46} This applied to asymptomatic cysts with typical imaging findings, including smooth, regular wall contours and no solid component.

Aspiration of the cyst is not a definitive treatment because it is usually not successful. Only complete removal of the cyst avoids recurrence. Spleen-conserving approaches are feasible for most cysts, unless they are centrally located. One attractive approach with very low morbidity is near total resection of the cyst wall, leaving just the part of the wall of the cyst attached to the spleen in situ (“unroofing” or “decapsulation”). This is associated with low morbidity, but radiologic recurrence in children may be >65\%\textsuperscript{47,48}; however, these recurrences are usually smaller than the original cyst, and many are asymptomatic and can be managed conservatively.\textsuperscript{47} In adults, reported long-term recurrence rates range from 20\% to 60\%.\textsuperscript{49-51} Although partial splenectomy has higher potential morbidity related to bleeding or ischemia of the remnant, it is becoming a more common option given that it allows resection of the cyst itself but leaves splenic tissue behind, maintaining immunologic function. Leaving at minimum 25\% of splenic tissue is thought to confer adequate immunologic function.\textsuperscript{52} This can also be done safely via the laparoscopic approach, as discussed below.

**Splenic Abscess**

Splenic abscesses tend to be rare, due to the spleen’s ability at fighting infections and bacteria. They are more frequently seen in areas with a high incidence of sickle cell anemia, with associated thrombosis of parenchymal
vessels and subsequent splenic infarction.

The major risk factors for such abscesses in the West are intravenous drug use, human immunodeficiency virus (HIV) infection, other hematogenous spread (endocarditis), splenic trauma, and contiguous spread. Endocarditis can be complicated with splenic abscesses in 5% of cases. These are often multiple abscesses similar to what is seen in other organs; the spleen is just a part of overwhelming sepsis. Most infections are polymicrobial and include such organisms as Staphylococcus, Salmonella, Escherichia coli, Proteus mirabilis, Streptococcus group D, Klebsiella pneumoniae, Peptostreptococcus, Bacteroides, Fusobacterium, Clostridium, Candida albicans, and Mycobacterium.

The symptoms are usually nonspecific, such as malaise, weight loss, left upper quadrant pain, and fever. Most patients have a leukocytosis, and an ultrasound, CT, or MRI study establishes the diagnosis of a splenic abscess. Treatment consists of broad-spectrum antibiotics and percutaneous drainage, which, if it fails, will require laparoscopic or open splenectomy. Many patients have multiple other abscesses in other organs. Antibiotic treatment should continue until the drains or percutaneous catheters have been removed. If the spleen has multiple abscesses, splenectomy may be required.

**Splenic Tumors**

Splenic masses may be identified during workup of symptoms or incidentally during other imaging. Some of these masses have a large cystic component (see Fig. 77-12). Management of such lesions may result in difficult clinical decision making as imaging alone does not always result in a definitive diagnosis. Often, these lesions may need to be followed serially, or if concerning, splenectomy should be considered. The underlying pathology may depend on referral patterns. In a series of 44 such cases, half of whom were symptomatic and treated surgically, 75% of lesions were benign while the remainder were malignant. In a similar study of 28 patients, the risk of a malignant diagnosis was significantly higher at 72%, although 25% of these patients had a previous history of lymphoproliferative disorder. There are increasing data on the use of image-guided splenic fine-needle aspiration to differentiate such masses, with low complication rates. Sensitivity and
specificity of such aspiration have been reported as 94% and 79%, respectively,\textsuperscript{58} with low risk of complications, even for core-needle biopsy.\textsuperscript{59}

**BENIGN NEOPLASMS**

Splenic neoplasms generally arise from the lymphoid or vascular elements of the spleen. They include a broad range of lesions, from benign (hemangioma, hamartoma, lymphangioma, and sclerosing angiomatoid nodular transformation) to intermediate (littoral cell angioma, hemangioendothelioma, and hemangiocytoma) to malignant (angiosarcoma). The more commonly found benign lesions are discussed here.

Hemangiomas are the most common benign neoplasms of the spleen with an incidence ranging from 0.02% to 16% and can be single or multiple.\textsuperscript{60} Most are now diagnosed incidentally during imaging for other pathology. Hemangiomas vary from well-circumscribed to irregular vascular proliferations. They consist of a benign overgrowth of nonencapsulated proliferation of new blood vessels of variable size, from capillary to cavernous formations. They are thought to be congenital in origin, and most are cavernous in nature. On CT scan, hemangiomas appear as homogeneous, hypodense, or multicystic lesions with variable calcification and peripheral enhancement. On MRI, they have high signal intensity on T2-weighted images with peripheral enhancement on delayed images.\textsuperscript{61} The potential for malignant transformation to angiosarcoma is not known but appears to be low.

The majority of splenic hemangiomas do not require surgical intervention. Most are asymptomatic. Splenectomy is reserved for tumors that become symptomatic due to size or consumptive coagulopathy. Although there has traditionally been concern about risk of spontaneous rupture or rupture with blunt trauma, a contemporary series from the Mayo Clinic reported no spontaneous rupture among 32 patients with splenic hemangioma, 80% of whom were entirely asymptomatic.\textsuperscript{60} Attempts at treatment using embolization of arterial branches or radiofrequency ablation have been reported, but more data are needed to understand their efficacy.

Sclerosing angiomatoid nodular transformation (SANT) is a benign vascular lesion first defined by Martel et al\textsuperscript{62} in 2004. SANT consists of altered red pulp trapped by nonneoplastic stromal proliferation.\textsuperscript{63} There is
often a central stellate scar. Patients are usually asymptomatic with a solitary splenic mass found incidentally on imaging. There is a 2:1 female predominance. Ultrasound shows a hypoechoic lesion. CT and MRI studies may show a central scar, enhancing capsule, and radiating bands corresponding to fibrosis.\textsuperscript{61,64} The lesion may have \textsuperscript{18}F-fluorodeoxyglucose (FDG) avidity on positron emission tomography (PET) scan.\textsuperscript{64} The average size in a case series of resected patients was 5.8 cm (range, 3.2-10.2 cm).\textsuperscript{65} Although SANT often displays characteristic radiologic findings, differentiation from other benign and malignant lesions may be challenging, and splenectomy may be required (Fig. 77-13).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{screenshot.png}
\caption{A 5.8 × 3.8 × 4.8 cm lesion located centrally in the spleen on magnetic resonance imaging. This was initially found incidentally on an ultrasound done for symptomatic gallstones. On positron emission tomography scan, the lesion was hypermetabolic with heterogeneous increased radiotracer accumulation, with a maximum standardized uptake value of 4.4. She underwent laparoscopic splenectomy and cholecystectomy. The pathology revealed sclerosing angiomatoid nodular transformation (SANT) in the spleen.}
\end{figure}

Littoral cell angioma (LCA) is a rare vascular tumor of the spleen. It is an
endothelial cell neoplasm arising from the cells lining the sinus channels of the splenic red pulp. These rare lesions express vascular and histiocyte-associated antigens. The autopsy incidence ranges from 0.03% to 14%. They are seen at any age range, with no sex-based predilection. Two forms of LCA are seen: diffuse multiple nodular LCA and the more rare solitary form. Imaging features on ultrasound vary widely from heterogeneous echotexture with no specific nodules to hyperechogenic-, hypoechoogenic-, or isoechoogenic-appearing lesions. A comparison between sonographic and pathologic features has shown that lesions with minimal blood-filled spaces appear as hypoechoic spaces, whereas lesions with lots of blood-filled spaces appear as hyperechoic spaces. On an unenhanced CT imaging study, nodular LCA lesions are not visible unless they have a hemorrhagic component. On a contrast CT in the portal venous phase, LCAs appear as low-attenuation lesions; LCAs are iso-attenuating on delayed images.

Although classified as benign, recent literature classifies LCAs as having uncertain biologic behavior. Malignant transformation to littoral cell angiosarcoma is very rare, but cases with dissemination to the liver and brain have been reported. An association with malignant lymphomas and other visceral organ cancers, including thyroid, colon, lung, pancreas, liver, brain, hematologic, ovarian, and testicular, has been reported. This leads to reluctance in classifying it as a completely benign lesion. In addition, LCA is also associated with various congenital and immunologic conditions, including inflammatory bowel disease, Wiskott-Aldrich syndrome, Epstein syndrome, lymphocytic colitis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis, Gaucher disease, myelodysplastic syndrome, chronic glomerulonephritis, and aplastic anemia.

The majority of patients are asymptomatic. Symptomatic patients present with abdominal pain, left upper quadrant fullness with satiety, splenomegaly, anemia, thrombocytopenia, or constitutional symptoms such as weight loss, anorexia, or fever of unknown origin. A preoperative diagnosis of LCA can be made with an image-guided fine-need aspiration or needle biopsy. Some authors recommend close follow-up, but given its small malignant potential and possible concomitant malignancies, splenectomy may be recommended. The potential for familial predisposition has been raised, and screening for splenic lesions in family members is suggested.

Lymphangiomias are congenital malformations thought to be due to
obstruction of the venolymphatic system (see Fig. 77-12B). Microscopically, these endothelium-lined spaces are filled with lymph and blood elements. The lesion may be focal or multiple, a small or large cystic mass, or may diffusely involve the spleen and account for splenomegaly. The diagnosis is made by ultrasound, CT scan, or MRI that reveals water-density cystic lesion(s) of the spleen. The lymphangioma may be isolated to the spleen or occur as a generalized lymphangiomatosis with multivisceral involvement and a poor prognosis. Symptoms, when present, are related to the size and mass effect of the lesion. Splenectomy is indicated for symptomatic lesions.

Inflammatory pseudotumor of the spleen is a reactive lesion characterized by a mixture of inflammatory cells and disorganized spindle cells. It is infiltrative in nature and may mimic malignant lymphoproliferative disease. These are seen in middle-aged and older patients, with a higher incidence in women. This tumor is typically found incidentally and is generally asymptomatic but may present with systemic symptoms such as abdominal pain, splenomegaly, or symptoms suggestive of malignancy such as fever, malaise, and weight loss. Imaging studies are nonspecific. The differential diagnosis includes lymphatic neoplasms, inflammatory granulomatous processes, hamartomas, hemangiomas, hemangioendotheliomas, and angiosarcomas. Although inflammatory pseudotumors are benign, no method with adequate sensitivity or specificity is available to make a definitive diagnosis. The diagnosis can be made via percutaneous fine-needle aspiration cytology, but splenectomy may be required to rule out malignancy if a diagnosis cannot otherwise be made.

Other benign lesions of the spleen are uncommon. Splenic hamartomas are uncommon, with autopsy series noting an incidence of 0.024% to 0.13%. They are solid but may have a cystic or necrotic component. Peliosis is not a true neoplastic lesion but a blood-filled cystic lesion without an endothelial lining that may be associated with focal, patchy, or diffuse involvement of the spleen. This lesion is likely reactive as it has been associated with steroids, oral contraceptives, immunosuppression medications, tuberculosis, renal disease, and malignancy. Other benign splenic tumors, such as angiomyolipoma, lipoma, hemangiopericytoma, and fibroma, are rare.

**PRIMARY MALIGNANT TUMORS**

Primary, nonlymphoid, malignant tumors of the spleen are exceedingly rare.
These include angiosarcomas, malignant fibrous histiocytomas, and plasmacytomas. Angiosarcoma is the most common nonlymphoid primary malignant neoplasm of the spleen. The clinical presentation may include abdominal pain, left upper quadrant abdominal mass, and constitutional symptoms. Metastasis is frequent and often involves the liver. Spontaneous rupture has been reported and is associated with a dismal outcome. Normocytic anemia is present in the majority of cases. Splenomegaly with hypersplenism is also seen. CT imaging often identifies a splenic lesion with central necrosis. The primary treatment is splenectomy. Cisplatin-based chemotherapy has also been used. However, even without rupture, splenic angiosarcoma holds a poor prognosis. Recent studies have reported 1-, 3-, and 5-year survival rates of 60%, 40%, and 40%, respectively.\(^\text{71}\)

**METASTATIC TUMORS**

Splenic metastasis of nonhematologic malignancies is rarely seen clinically and usually represents widespread dissemination of disease. In a review of a German oncologic database, only 0.002% of patients with a malignancy developed reported splenic metastasis, with isolated splenic metastasis being extremely rare.\(^\text{72}\) Despite the rarity of clinically evident splenic metastasis, postmortem evidence is reported to be higher, although the exact prevalence of this is debated, with older literature reporting rates as high as 34%, while contemporary reports put this rate at approximately 3%.\(^\text{73}\) The most frequent sites of primary tumors with splenic metastasis are lung, colorectal, ovary, melanoma, and breast.\(^\text{74}\)

The diagnosis of malignancy can be confirmed by PET scanning, although percutaneous biopsies for isolated lesions can also be performed (Fig. 77-14).\(^\text{75}\) Splenectomy may be indicated to treat isolated metastatic disease, especially for patients with chemosensitive tumors or in whom cytoreductive surgery can improve outcomes.\(^\text{74}\)
FIGURE 77-14 The patient was found to have a splenic lesion on CT of the chest in the context of a right lung cancer. Percutaneous biopsy revealed adenocarcinoma consistent with lung primary. She underwent splenectomy for this isolated metastasis.

HEMATOLOGIC DISORDERS

In 1887, Sir Thomas Spencer Wells, the renowned gynecologist, performed a therapeutic splenectomy for what proved to be hereditary spherocytosis. The first splenectomy for autoimmune hemolytic anemia (AIHA) was performed in 1911 by Micheli. Six years later, Schloffer, at the suggestion of a medical student, Kaznelson, performed a splenectomy for idiopathic thrombocytopenic purpura.¹ The indications for splenectomy in hematologic disease are continuously evolving, but there are many conditions for which splenectomy plays an important role. The most common hematologic indications for splenectomy are immune thrombocytopenia purpura, hereditary spherocytosis, and AIHA.

ANEMIAS

Splenectomy is indicated for specific cases of anemia. The major categories
of anemia that benefit from splenectomy are those caused by the following:

- Membrane abnormalities: Hereditary spherocytosis and elliptocytosis
- Enzyme defects: Pyruvate kinase deficiency
- Hemoglobinopathy: Thalassemias and sickle cell
- AIHA

**Hereditary Spherocytosis**

Hereditary spherocytosis (HS) is a hemolytic anemia that results from a genetic defect or deficiency in one of the components of the red cell cytoskeleton. It results in spherically shaped erythrocytes on blood smear, reticulocytosis, and splenomegaly. HS is transmitted as an autosomal dominant trait but occurs sporadically in rare instances. HS is the most common cause of familial chronic hemolytic anemia in North America and Northern Europe, with an incidence of 1 to 5 in 10,000 births, or even higher if mild cases of osmotic fragility are included.\textsuperscript{76}

Abnormalities of the proteins in the red cell membrane (spectrin, ankyrin, band 3, and/or protein 4.2) cause increased osmotic fragility and changes in morphology, resulting in the spherical shape and decreased deformability. The red cell membrane change results in splenic trapping of the abnormal cells in the microcirculation, followed by their destruction by phagocytosis.\textsuperscript{77} Thus, the spleen plays a critical role in the pathophysiology of HS, as it is the main site of hemolysis. Cells that escape the spleen on first passage are more susceptible to trapping and destruction during each successive passage.

The salient clinical features include anemia, jaundice, and splenomegaly, with spherocytes on blood smear, increased osmotic fragility, and positive family history.\textsuperscript{77} The severity of disease varies widely and is classified as mild, moderate, and severe based on hemoglobin, bilirubin, and reticulocyte count (Table 77-3).\textsuperscript{78,79} Approximately 30% of cases are mild, maintaining near-normal hemoglobin and bilirubin levels and compensatory reticulocytosis. Patients with severe spherocytosis are transfusion dependent with baseline hemoglobin level less than 6 g/dL.
SPLENECTOMY

<table>
<thead>
<tr>
<th>Classification</th>
<th>Trait</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/L)</td>
<td>Normal</td>
<td>110-159</td>
<td>80-120</td>
<td>60-80</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>Normal (&lt;3%)</td>
<td>3-6</td>
<td>&gt;6</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>&lt;17</td>
<td>17-34</td>
<td>&gt;34</td>
<td>&gt;51</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Not required</td>
<td>Usually not necessary during childhood and adolescence</td>
<td>Necessary during school age before puberty</td>
<td>Necessary; delay until age 6 if possible</td>
</tr>
</tbody>
</table>

The disease severity is related to the degree of red cell cytoskeleton protein deficiency, particularly spectrin shortage. The jaundice usually parallels the severity of anemia and generally is not intense. It is related to increased red cell destruction, resulting in abundant bile pigment that cannot be cleared by the liver. Most patients have mild to moderate spleen enlargement, but splenomegaly alone is not an indication for surgery. Increases in splenic size in patients with HS may be seen in the presence of acute infection. Periodic worsening of the associated anemia and jaundice may be seen, often following infection, emotional stress, fatigue, or prolonged exposure to cold. Gallstones are the most common complication of HS but are unusual in children younger than age 10 years. The gallstones are generally pigmented.

Splenectomy is effective in reducing the hemolysis associated with HS but at the price of a lifelong risk of severe sepsis from encapsulated organisms, and emerging evidence links splenectomy to late vascular complications such as pulmonary hypertension and atherosclerosis.\(^7^9\) Splenectomy should not be recommended simply due to the diagnosis of HS but is based on the severity of anemia (see Table 77-3). Failures are uncommon and often reflect missed accessory spleens, which can be identified using radiocolloid liver-spleen scans.\(^7^7\) The preferred approach is laparoscopic as it is associated with less postoperative morbidity and pain. Because of the increased risk of serious postsplenectomy sepsis among young children, with a subsequent mortality rate of 50% to 80%, splenectomy is reserved preferably for patients older than 6 years\(^7^9\) and should not be done in children younger than age 3, even if chronic transfusions are needed.\(^7^8\)

Concern over postsplenectomy sepsis risks, especially in young children, has led to investigation of the effectiveness of partial splenectomy to control hemolysis while leaving some functional spleen behind for immunologic...
Either the lower pole, based on the gastroepiploic, or the upper pole, based on the uppermost short gastrics, is preserved. This approach has somewhat less effective hemolytic control. A recent review of moderate-quality evidence reported that partial splenectomy resulted in increases of hemoglobin of 2.3 to 3.9 g/dL, compared to 4 to 5 g/dL with total splenectomy, but both resulted in decreased reticulocyte counts, anemic crises, and transfusions. Most studies suggested that partial splenectomy maintained splenic immune function and phagocyte activity, but there was a lack of longer term studies comparing adverse events such as sepsis or vascular complications. A multi-institutional review of 62 children of all ages undergoing a partial splenectomy showed a good response with no postsplenectomy sepsis with up to 18 years of follow-up and only 4.8% of patients requiring completion splenectomy. They noted that splenic remnant regeneration correlated with the degree of recurrence of anemia and clinical symptoms, but this is not a consistent finding. The Splenectomy in Hemolytic Anemia (SICHA) Consortium Registry compared outcomes after total and partial splenectomy. Excellent hematologic response through 1 year was seen after both procedures, with a more robust response (ie, greater increase in hemoglobin) after total splenectomy. Guidelines conclude that partial splenectomy may be beneficial, but further follow-up studies are required.

Concomitant cholecystectomy is performed if gallstones are present. Prophylactic cholecystectomy in the absence of stones is not required because patients no longer develop pigmented stones after splenectomy. In a cohort of patients younger than 18 years, none developed cholelithiasis after splenectomy over a mean follow-up of 15 years. The presence of Gilbert disease increases the risk of subsequent gallstones. On the other hand, symptomatic gallstones have traditionally been an indication for concomitant splenectomy in children, due to the concern for the development of future biliary duct stones. This is now controversial in children with mild disease. In a series of 16 patients with mild HS having cholecystectomy without splenectomy, only 3 required subsequent splenectomy.

**Hereditary Elliptocytosis**

Hereditary elliptocytosis is a red cell hemolytic anemia affecting 3 to 5 of
every 10,000 people with a heterogeneous array of genotypes and
phenotypes. It is more common in people of African and Mediterranean
origin, presumably because it results in some resistance to malaria. \(^{77}\) It is a
group of erythrocyte disorders that have in common the presence of
elongated, oval, or elliptically shaped RBCs on the peripheral blood film.
Most are transmitted as an autosomal dominant trait. Most patients are
asymptomatic or have a mild form of the disease with compensated
hemolytic anemia, as the defects often do not significantly shorten the red
cell life span despite striking abnormalities seen on blood film. The presence
of hemolysis often is a familial characteristic, and it has been suggested that
excessive hemolysis occurs only when the gene for elliptocytosis is present in
the homozygous form or is modified in some other way. The signs and
symptoms are related directly to the severity of hemolysis resulting from the
extent of decreased membrane stability and subsequent loss of membrane
surface area. Occasionally an acute hemolytic episode may be precipitated by
infection. The clinical syndrome is indistinguishable from that described for
HS. Gallstones and chronic leg ulcers have been reported in symptomatic
patients. The spleen is usually palpably enlarged in symptomatic cases.
Diagnosis is established by the smear.

Therapy is rarely required. Indication for splenectomy is the same as for
HS and is almost always followed by lasting effects. Decreased hemolysis
and corrected anemia result from longer circulatory life span of the red cells,
although the morphologic abnormality of the RBC remains unchanged.
Associated cholelithiasis should be managed as in HS.

**Pyruvate Kinase Deficiency**

Pyruvate kinase deficiency is the most common RBC enzyme deficiency
causing congenital nonspherocytotic hemolytic anemia. It is an autosomal
recessive condition that has a much lower frequency than glucose-6-
phosphatase deficiency (G6PD); however, it a more common cause of anemia
because G6PD patients rarely suffer hemolysis.

Clinical manifestation varies from transfusion-dependent anemia to
compensated chronic hemolysis. Splenomegaly is common. There is no
curative therapy. Splenectomy has a role in transfusion-dependent individuals
and can reduce or even abolish the need for transfusion. \(^{89}\) As with other
children being evaluated for splenectomy, the procedure should be delayed until after age 3 due to the immunosuppressive effect of the surgery.

**Thalassemia**

Thalassemia (Mediterranean anemia) is a congenital disorder transmitted as a dominant trait in which the anemia is primarily the result of a defect in hemoglobin synthesis. Thalassemias are the most common monogenetic disease in man and have been referred to as *Cooley anemia, erythroblastic anemia, and target-cell anemia*. The disease is classified as alpha, beta, and gamma types, determined by the specific defect in the synthesis of the relevant globulin chain of the adult hemoglobin. As a consequence of the defect, there is imbalance in production of globulin chains with resultant formation of atypical hemoglobin proteins that can lead to intracellular precipitates (Heinz bodies) that contribute to premature red cell destruction. The hemoglobin-deficient red cells are small, thin, and misshapen, and have a characteristic resistance to osmotic lysis. Over 200 genetic mutations have been identified that lead to β-thalassemia.⁹⁰ The high prevalence and diversity of the thalassemias are related to heterozygote protection against malaria.⁹¹

In the United States, most patients suffer from β-thalassemia, and there is a quantitative reduction in the rate of β-chain synthesis, resulting in a decrease in hemoglobin A. The characteristic feature is the persistence of hemoglobin F and a reduction in hemoglobin A. Precipitation of the excess α chains in erythroid precursors causes dyserythropoiesis and results in membrane defects and hemolysis in mature RBCs.⁹² Gradations of the disease range from heterozygous thalassemia minor to severe homozygous thalassemia major. The latter is manifested by chronic anemia, jaundice, and splenomegaly.

Patients with homozygous thalassemia major usually present with clinical manifestations in the first year of life. In addition to the anemia and consequent pallor, failure to thrive, gastrointestinal symptoms, and feeding problems are also seen. With adequate transfusions, the children grow and develop normally, avoiding the typical features of Cooley anemia, including retarded body growth and enlargement of the head, leg ulcers, and infections.⁹¹ Some patients present with repeated episodes of left upper
quadrant pain related to splenic infarction. Cardiac dilatation occurs, and in advanced stages, there is subcutaneous edema and effusion into serous cavities. Intercurrent infections occur frequently, often leading to death in more severe cases. These infections may be associated with aplastic crises. Gallstones have been reported in up to 24% of cases.

Therapy is directed only at symptomatic patients, those having thalassemia major or intermedia. In these patients, transfusions are usually required at regular intervals. Because most children with thalassemia major accommodate to low hemoglobin levels, transfusions are given when the hemoglobin level is less than 10 g/dL. By age 10, complications develop related to iron overload, including cardiomyopathy, liver fibrosis, and endocrine disturbances. Iron overload is reduced using iron chelators. Stem cell transplantation from an human leukocyte antigen–identical donor is an exciting advance with a high rate of remission, especially in young, fit patients prior to the development of complications from iron overload or viral hepatitis.

Although splenectomy does not influence the basic hematologic disorder, it may eliminate or reduce the hemolytic process responsible for accelerated destruction of normal donor red cells within the patient’s circulation, and this reduces transfusion requirements. In general, the best results associated with splenectomy have been obtained in older children and in young adults with large spleens in whom excessive splenic sequestration of red cells has been demonstrated. Splenectomy should be avoided in children younger than age 5 years. Occasionally, splenectomy may be indicated because of mass effect symptoms associated with marked splenomegaly or repeated episodes of abdominal pain due to splenic infarction.

**Sickle Cell Disease**

Sickle cell anemia, first reported in 1910, is a hereditary disorder of hemoglobin characterized by the presence of crescent-shaped erythrocytes that, because of a lack of deformability, are trapped in the splenic cords. In this disorder, the normal hemoglobin A is replaced by hemoglobin S. Under conditions of reduced oxygen tension, hemoglobin S molecules undergo crystallization within the cell, which elongates and distorts the cell. The sickle cells increase the blood viscosity and circulatory stasis, thus
establishing a vicious cycle. Although the sickle cell trait occurs in approximately 9% of the black population, the majority of patients are asymptomatic. Sickle cell anemia is observed in 0.3% to 1.3% of blacks. Many body systems can be affected by sickle cell disease. Depending on the vessels affected by vascular occlusion, the patients may have bone or joint pain, osteomyelitis, priapism, neurologic manifestations, or skin ulcers. Abdominal pain and cramps due to visceral stasis are frequent.

The spleen is commonly affected in these patients. Sickling occurs so rapidly that blood flow through both the fast and slow compartments of the spleen is obstructed; as a consequence, a series of microinfarcts develop and eventually lead to “autosplenectomy.” In most adult patients, only a fibrous area of the spleen remains, but autosplenectomy is preceded by splenomegaly in about 75% of patients. Calcification may occur with autoinfarction (Fig. 77-15). Such functional asplenia is defined and detected by the presence of Howell-Jolly bodies in the blood film and can be confirmed by absence of technetium-99m ($^{99m}$Tc) splenic uptake. Patients are subsequently at risk of developing infection by encapsulated organisms such as *Streptococcus pneumoniae*, due to impaired filtration and antibody production of the spleen. Rarely thrombosis of the splenic vessels may result in the complication of splenic abscess manifested by splenomegaly, splenic pain, and spiking fever. Percutaneous drainage of such abscesses may be attempted, but it may require a splenectomy.
For most patients with sickle cell anemia, only palliative therapy is available. Adequate hydration and partial exchange transfusion may help the crisis. Randomized multicenter studies have shown a role for hydroxyurea in treatment of adults with sickle cell disease. Such treatment leads to reduction in frequency of painful crisis, hospitalization, and transfusion. The beneficial effects are in part due to an increase in hemoglobin F levels, although the mechanism underlying this process is not known. Hydroxyurea is therefore recommended in patients with 3 or more crises per year. Other hemoglobin F–inducing agents and stem cell transplant are also currently under investigation.

There are 2 situations in sickle cell anemia where the spleen is a pathologic red cell reservoir, and splenectomy may have a role. The first is a form of chronic hypersplenism that usually occurs in childhood or adolescence and is manifested by reduced red cell survival, leukopenia, and thrombocytopenia. In these patients, for some unknown reason, there is a failure to undergo autosplenectomy. In this rare circumstance, splenectomy will correct the leukopenia and thrombocytopenia and will also increase the
rate of red cell survival and can lead to reduced transfusion requirement. The second abnormality has been termed acute splenic sequestration and is marked by sudden splenic enlargement associated with worsening anemia and profound hypotension. It usually occurs in the first 5 years of life in a homozygous child; streptococcal pneumonia infection may act as a precipitating event in these patients. The acute splenic sequestration is usually effectively treated with packed red cell transfusion. If there is a propensity for recurrence, splenectomy may be indicated.

**Immune Hemolytic Anemia**

The first description of this disease is credited to Chauffard and Troisier who, in 1908, demonstrated autohemolysins in the serum of several patients with acute hemolytic anemia. Three years later, Micheli performed the first planned, successful splenectomy, thus stimulating the application of splenectomy for hematologic disease.

Immune hemolytic anemia (IHA) is a disorder in which immunoglobulin G (IgG) and/or IgM antibodies bind to erythrocyte surface antigens and stimulate erythrocyte destruction. This occurs through the complement and reticuloendothelial systems. IHA is classified as autoimmune, alloimmune, or drug-induced. Alloimmune hemolytic anemia occurs only after exposure to allogeneic erythrocytes, such as through blood transfusion, pregnancy, or transplant. There is no antibody reactivity against autologous red cells. Acute hemolysis after transfusion is estimated to occur in 0.0003% to 0.0008% of patients, and a delayed response is seen in 0.05% to 0.07%. Drug-induced IHA occurs as drug-induced antibodies recognize red cell antigens or erythrocyte-bound drug. More than 150 drugs have been associated, including methylprednisolone, ibuprofen, penicillin, and second- and third-generation cephalosporin. Drug-induced IHA should resolve with cessation of the medication in question but may require corticosteroids and have a protracted recovery.

Autoimmune hemolytic anemia (AIHA) is estimated to occur in 1 per 100,000 per year, with a prevalence of 17 per 100,000. It is an antibody-mediated process that involves IgG or IgM antibodies. In cases of IgG-mediated disease, antibodies bind to the erythrocyte and are recognized by the Fc receptors of macrophages and other phagocytic cells of the
reticuloendothelial system. In contrast to IgG antibodies, IgM antibodies readily activate the classical complement pathway and may lead to intravascular hemolysis. Additionally, IgM-bound erythrocytes may undergo extravascular hemolysis, particularly in the liver.

Both warm and cold antibodies have been reported. Warm antibodies react best at 98.6°F (37°C), account for the approximately 70% of cases, and are mainly due to IgG. Secondary causes of warm AIHA have been reported, most notably in the context of lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL), lupus, infectious mononucleosis, HIV, and autoimmune hepatitis. The presentation of warm AIHA is variable and includes vague constitutional symptoms consistent with anemia, such as weakness and dizziness. Additionally, fever, abdominal pain, cough, and bleeding may be seen. Symptoms vary with the severity of the hemolysis. Mild jaundice is often present. Splenomegaly is seen in approximately half of cases, and 25% may have associated cholelithiasis. While reticulocytopenia may occur early in the disease prior to adequate marrow response, reticulocytosis and elevated mean cell volume (MCV) are generally seen. Mild to moderate indirect hyperbilirubinemia and elevated lactate dehydrogenase (LDH) are often seen. Platelets are usually normal, but occasionally, AIHA and immune thrombocytopenic purpura occur together (Evan syndrome). More than 95% of patients with warm AIHA have a positive Coombs test (direct antiglobulin test), which indicates that antibodies or complement system are bound to the red cell surface antigens in vivo.

Therapy is guided by the severity of the hemolysis, with first-line treatment being corticosteroids. Prednisone therapy (1-1.5 mg/kg/d) is maintained for 3 weeks, with rapid response being the norm. If a satisfactory response is achieved, the steroid is gradually tapered over 6 months to avoid relapse. Approximately 80% of patients have a partial or complete response to steroids, but only 20% to 30% are cured. In nonresponders or those requiring maintenance steroid dose greater than 10 to 15 mg of prednisone daily, second-line therapy should be considered. These options include splenectomy or rituximab, a monoclonal antibody against CD20 found on the surface of B cells. Splenectomy can lead to good short-term results, with early response in approximately 70% of patients and cure in 20% to 60%. Drawbacks are lack of a reliable way to predict outcome to splenectomy, risk of long-term sepsis, and possible increased risk of thrombosis. Rituximab is increasingly used as second-line treatment, with response rates that appear
similar to splenectomy. There are no randomized trials comparing second-line therapies, so the choice of splenectomy or rituximab is based largely on patient and physician preferences and availability of newer medications.96

In contrast, cold agglutinin disease is due to IgM, resulting in intravascular hemolysis. Acute cold agglutinin disease is due to infections, whereas the chronic form occurs in lymphoproliferative or neoplastic diseases.96 Primary cold agglutinin disease may only present with mild anemia and may respond favorably to cold exposure avoidance. Corticosteroids are less effective than in warm AIHA and require high doses. Rituximab is recommended as first-line therapy, with a 60% response rate. Plasmapheresis offers a temporary response in acute hemolytic crises. Splenectomy is ineffective in cold agglutinin syndrome.

Paroxysmal cold hemoglobinuria is an uncommon form of AIHA and is generally self-limited and treated with supportive care. Most cases occur in children, usually after a viral illness. Corticosteroids are often given to children with severe anemia but with unclear effectiveness.

**PURPURAS**

**Immune Thrombocytopenia**

Immune thrombocytopenia (ITP) is the most common hematologic indication for splenectomy. The terminology of primary ITP replaces the previous term idiopathic thrombocytopenia purpura.99 ITP is an acquired disorder in which platelets are destroyed by circulating antiplatelet antibodies, often IgG antibodies targeted against glycoprotein IIb/IIIa proteins. Antibody-coated platelets bind to antigen-presenting cells via Fc receptors primarily in the spleen, leading to platelet destruction. An alternate mechanism for platelet destruction is via T-cell–mediated lysis. The spleen is the source of antiplatelet antibody production as well as the major site of platelet-antiplatelet antibody complex destruction by macrophage-induced phagocytosis. Antiplatelet glycoprotein antibodies also impair platelet production in the bone marrow by megakaryocytes, impairing the ability to compensate for the increased rate of platelet removal from the blood.100,101

The diagnostic criteria for primary ITP are a platelet count less than 100 ×
without an obvious initiating or underlying cause, whereas secondary ITP encompasses ITP associated with underlying diseases, infections, or medications. The incidence is estimated to be between 1.6 and 4 per 100,000 per year. Female patients outnumber males 3 to 1.

Many patients are diagnosed incidentally on routine evaluations. Bleeding in ITP is usually not severe, even with very low platelet counts. Mucocutaneous bleeding involving the skin, oral cavity, and gastrointestinal tract is the most common clinical presentation. Central nervous system (CNS) bleeding is estimated to occur in 1.4% (95% CI, 0.9%-2.1%) of adult patients with chronic ITP generally with platelet counts <10 to 20 × 10⁹/L. Older age is an identified risk factor for major bleeding. Risk of hemorrhagic death is very low and estimated to be 0.02 to 0.04 cases per adult patient-year at risk. The spleen is typically normal size. Generally, there is no significant anemia or leukopenia unless the ITP occurs in conjunction with AIHA (Evan syndrome).

ITP is often associated with other immune disorders, such as systemic lupus erythematosus. The workup should include examination of peripheral blood smear to exclude other causes of thrombocytopenia. Screening for HIV, hepatitis C virus (HCV), and *Helicobacter pylori* is recommended in adults. If any of these infectious etiologies are identified, therapy should be aimed at treating the underlying process rather than platelet count per se. *H pylori* eradication is associated with response rates of approximately 50%. A bone marrow examination is not necessary for diagnosis in patients with history, physical exam, complete blood count, and blood smear typical for ITP.

ITP in children is typically self-limited and rarely requires surgical therapy. The disease in adults is usually more persistent with a low spontaneous remission rate (9%) and requires medical and possibly surgical treatment. Treatment is generally not indicated in those with platelet counts >30 × 10⁹/L and no bleeding complications. The goal of all medical therapies is to increase platelet count to a safe level and not to cure. Treatment in newly diagnosed ITP is aimed at rapid increase of platelets to treat or prevent bleeding. First-line treatment is usually a short course of corticosteroids (1 mg/kg/d for 2-3 weeks and rapidly tapered) and/or intravenous immunoglobulin infusion if a more rapid increase in platelets is needed. Most patients respond within 1 week, but platelet counts
decrease again when the dose is tapered, with long-term remission in only 5% to 30% of patients.¹⁰² A shorter course of high-dose dexamethasone may also be effective.¹⁰⁶ Intravenous immunoglobulin (IVIg) or anti-Rh(D) (in Rh-positive patients) can be used if corticosteroids are contraindicated.

In adults who do not respond to corticosteroids or with chronic ITP who require more than a minimal dose of corticosteroids to maintain safe platelet counts, second-line therapy is indicated. The objective of second-line therapy is to provide long-term and durable results. Splenectomy remains the most effective single therapy for ITP, with a complete or partial response rate of >80% and a cure rate of about 60% at 10 years.¹⁰⁸,¹⁰⁹ In most patients, the platelet count rises to >100 × 10⁹/L within 7 days. Rarely, platelet normalization is more gradual over a period of months. Indications for splenectomy include patients who fail to respond to first-line therapies, who recur after steroid taper, who respond to medical therapy but cannot tolerate the side effects, or who develop intracranial bleeding or profound gastrointestinal bleeding and do not respond to intensive medical treatment.

The use of splenectomy as second-line treatment is declining, as new second-line therapies, such as rituximab and thrombopoietin receptor (TPO-R) agonists, emerge.¹¹⁰ While initial response rates with rituximab are >50%, long-term response after 5 years is <20%.⁹⁹ In a recent randomized trial comparing rituximab to placebo in corticosteroid-unresponsive patients, there was no significant difference in the incidence of treatment failure at 18 months (58% in the rituximab group and 69% in the placebo group).¹¹¹ There are also safety concerns with rituximab including multifocal leukoencephalopathy and hypogammaglobulinemia, and it is predicted that the use of rituximab will decline with the availability of thrombopoietin agonists.¹¹² TPO-R agonists (eg, romiplostim and eltrombopag) are a new class of drugs that increase platelet production at the megakaryocyte level. They are well tolerated, and there is accumulating evidence regarding their efficacy. There are no direct comparisons between splenectomy, rituximab, and TPO-R as second-line therapies.⁹⁹ The American Society of Hematology 2011 guidelines recommend splenectomy as initial second-line therapy, with TPO-R or rituximab suggested for patients in whom splenectomy is contraindicated or who relapse after splenectomy.¹⁰⁶

In patients who do not respond to splenectomy or who relapse, residual splenic tissue should be ruled out,¹⁰² especially if the blood smear does not
show evidence of splenectomy (ie, no pitting or Howell-Jolly bodies in erythrocytes). Investigations include radionuclide scanning and MRI. These may be located in unusual or difficult-to-access locations including intrapancreatic locations, potentially requiring distal pancreatectomy. Removal of the residual tissue is recommended and can be done using laparoscopic techniques, which are facilitated using localization adjuncts. Reported response rates vary widely, with a recent series reporting a 50% response rate in 10 adult patients at 1 month.

Approximately 15% of patients fail to respond to splenectomy, and another 20% of responders relapse weeks to months later. Several factors that may predict response to splenectomy have been proposed including a response to IVIg and steroids, preoperative platelet count, patient age, and duration of medical therapy are not predictive of response. Indium-labeled autologous platelet scanning may be the most sensitive predictor but is only available presently as a research tool. When the scan demonstrates splenic platelet destruction, the response rate to splenectomy is 90%.

The laparoscopic approach to splenectomy is well suited for ITP because of the normal size of the spleen. While long-term outcomes are similar, a systematic review of 135 case series reported lower rates of complications (9.6% vs 12.9%) and mortality (0.2% vs 1%) after laparoscopic compared to open splenectomy. Retrospective studies in patients with ITP have demonstrated reduced postoperative pain, less analgesic use, and shorter hospital stay in those undergoing laparoscopic splenectomy compared to open splenectomy. Preoperative preparation with corticosteroids or IVIg is used to attempt to increase platelet counts because patients with platelet counts <20 × 10^9/L may be at higher risk of complications. However, in some patients, it may not be possible to increase platelet counts, and splenectomy can be done safely in ITP despite very low platelet counts. Platelets should be available for patients with platelet counts <20 × 10^9/L and transfused intraoperatively if there is bleeding after the splenic hilum is clamped. Avoidance of splenic injury that may result in splenosis and assessment of the abdominal cavity for accessory spleens are critical to success of splenectomy for ITP.

**Thrombotic Thrombocytopenic Purpura**
Thrombotic thrombocytopenic purpura (TTP) is a rare type of thrombotic microangiopathy, a family of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis. Other forms of thrombotic microangiopathy include typical hemolytic uremic syndrome (HUS) caused by enteric infection-causing diarrhea, atypical HUS that occurs without a predisposing cause, and secondary thrombotic microangiopathy, an infrequent complication seen in different settings including disseminated cancer, systemic infection, drugs, transplantation, and other conditions. The different kinds of thrombotic microangiopathies may be difficult to distinguish because they have overlapping clinical features, but their pathogenesis and prognosis differ. In patients with TTP, neurologic symptoms predominate, whereas in those with HUS, renal complications are the dominant symptom. TTP is recognized as the pentad of microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic disturbance, and renal dysfunction. Most cases of TTP are caused by autoantibodies to ADAMS13, a metalloprotease required for cleavage of von Willebrand factor. TTP is a microvascular disorder affecting arterioles and capillaries with venule sparing. Platelet microthrombi cause partial vessel occlusion with overlying endothelial proliferation and subintimal hyalinization. Subsequent erythrocyte damage occurs during passage through the narrowed vascular channels with abnormal forms (especially schistocytes) seen on peripheral blood smear. Marked platelet trapping occurs, namely in the spleen, with resultant thrombocytopenia (<20 \times 10^9/L). There may be a profound decrease in platelets within hours of onset. Petechial hemorrhage and, more rarely, epistaxis, retinal hemorrhage, gastrointestinal and genitourinary bleeding, and hemorrhagic stroke may be seen. However, it is more usual to see no bleeding even with severe thrombocytopenia partly because of the thrombotic nature of the disease. Other clinical manifestations include fever, general malaise and flu-like symptoms, headache, altered mental status, focal neurologic deficits, hematuria, and renal failure. The neurologic changes may be severe, such as coma, prompting emergent therapy.

Since the advent of plasma exchange therapy for TTP, which replaces stores of ADAMS13 and removes the antibody inhibitors, mortality for the once uniformly fatal disease has decreased markedly to 10% to 20%. Concomitant high-dose steroids are used. Daily therapy is conducted until the hemolytic process is stabilized and the thrombocytopenic and neurologic
complications subside. Plasma exchange is then tapered. Rituximab is beneficial for those with refractory or relapsing disease.\textsuperscript{120} Splenectomy is considered for refractory cases or those with recurrent disease after multiple plasma exchanges with a 70% remission rate.\textsuperscript{121}

**HEMATOPOIETIC NEOPLASMS AND LYMPHOMAS**

The classification of such malignancies, including lymphomas, leukemias, and myeloproliferative neoplasms, has evolved extensively over the past decade with the introduction of immunophenotyping and cytogenetics. Many tumor subtypes that were initially thought to be the same have been subdivided into groups with different management and prognosis. The 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid malignancies has provided a framework for classification of these diseases, which encompasses over 65 different types of tumor. A detailed description of this classification is beyond the scope of this chapter. In general, however, these neoplasms fall into 3 categories:\textsuperscript{122}

*Myeloid neoplasms:* Derived from bone marrow progenitors that form erythrocytes, granulocytes (neutrophils, basophils, eosinophils), and megakaryocytes.

*Lymphoid neoplasms:* Derived from cells that form T and B lymphocytes. When such neoplasms presented with predominantly bone marrow and blood involvement, they were referred to as *leukemia*, whereas those presenting with a mass were referred to as *lymphoma*. In the new classification, however, with new knowledge about tumorigenesis and the fact that lymphomas can present or evolve to a leukemia picture and that leukemia can present as a mass, more emphasis has been placed on cell of origin. This classification method based on cell type only, however, provides no information on clinical behavior of tumors. Some have therefore added a clinical classification to further group lymphomas as indolent (survival without treatment of years), aggressive (survival without treatment of months), highly aggressive (survival of untreated tumor of weeks), and Hodgkin lymphomas, which is generally regarded as a distinct entity with excellent prognosis.
Histiocytic/dendritic neoplasms: Derived from cells that develop into antigen-presenting cells such as dendritic cells and macrophages.

Indications for surgical intervention have evolved over the years as our knowledge and therapeutic options have expanded. Below is a brief overview, concentrating on situations where a splenectomy may be indicated.

**Myeloid Neoplasms**

These tumors are generally subdivided into 3 categories: *acute myeloid leukemias*, for which there is little surgical role, and *myelodysplastic syndrome* and *myeloproliferative disorders*.

*Myelodysplastic syndrome* is a group of disorders that is associated with ineffective blood production and risk of transformation to acute leukemia. Again, there is little indication for splenectomy or surgery in this group of patients.

In *myeloproliferative disorders*, there is proliferation of 1 or more of the myeloid lineage cells, with increases in the numbers of 1 or more of the peripheral blood elements. There is usually an associated mutation that causes increase in tyrosine kinase– and growth factor–dependent proliferation of bone marrow elements. Examples of such mutations include the *BCR-ABL* fusion gene in chronic myeloid leukemia. Other diseases in this category include polycythemia vera, essential thrombocythemia, and primary myelofibrosis. The presenting symptoms include symptomatic splenomegaly and anemia.

Although splenectomy does not alter the course of these diseases, it may be indicated for transfusion-dependent anemia or thrombocytopenia or symptomatic splenomegaly. There may be massive splenic enlargement with myeloproliferative disorders causing pain, early satiety, and weight loss. Most patients will benefit from the procedure, with approximately half of transfusion-dependent patients becoming transfusion independent, resolution of constitutional and mechanical symptoms, and improved thrombocytopenia. However, the morbidity associated with splenectomy for myeloid neoplasms makes it a high-risk procedure due to risks of bleeding, infection, portal vein thrombosis, and reoperation. Although effective for relief of symptomatic splenomegaly in most patients and to decrease transfusion requirements, a recent single-institution series of
splenectomy for myeloid neoplasms reported a 30-day mortality of 18% and a median survival of only 9 months that had not improved over time. Those with preoperative anemia and thrombocytopenia were at increased risk.\(^{124}\)

**Lymphoid Neoplasms**

Staging laparotomy in cases of Hodgkin lymphoma was once considered the key to determine the extent of abdominal involvement with stage I to II supradiaphragmatic disease and critical in determining the best therapy for patients. Those with disease limited to above the diaphragm were treated with radiation, while others received radiation and chemotherapy. Advances in imaging technology, including CT of the chest, abdomen, and pelvis, and 18-fluorodeoxyglucose PET, are now used for staging, and because chemotherapy is used in all stages, surgery is no longer performed to detect subclinical disease.\(^{125}\)

Non-Hodgkin lymphoma is the most common malignant neoplasm involving the spleen and the most common indication for splenectomy in malignancy in more recent case series. The spleen is involved in approximately 30% to 40% of patients, usually as a result of spread from other sites.\(^{126}\) Primary splenic lymphoma, confined to the spleen, is an uncommon presentation seen in fewer than 2% of patients with non-Hodgkin lymphoma.\(^{127}\)

**Indications for Splenectomy in Lymphoproliferative Disorders**

With new classifications of these disorders and variability in clinical presentation and treatment, the decision for splenectomy requires close collaboration with the hematologists and oncologists. In general, splenectomy is indicated for the following:

- Treatment of symptomatic splenomegaly: abdominal fullness, pain, early satiety, and constitutional symptoms
- Treatment of hypersplenism, defined as blood cytopenias in the setting of splenomegaly
- Treatment or tissue diagnosis when the spleen is the only or main site of
disease

Between 25% and 55% of patients with chronic lymphocytic leukemia (CLL) have palpable splenomegaly.\textsuperscript{128} Splenectomy may improve cytopenias in advanced CLL, with a success rate of about 50%.\textsuperscript{129} In patients with hemoglobin level of less than 10 g/dL or platelet count less $<50 \times 10^9$/L, splenectomy not only improves hematologic parameters but also may offer survival advantage compared to those who receive chemotherapy alone.\textsuperscript{130} Splenectomy is also indicated to treat refractory or recurrent AIHA or thrombocytopenia that may occur in CLL.

Splenic marginal zone lymphoma is a rare type of non-Hodgkin lymphoma that presents with splenomegaly without peripheral lymphadenopathy, cytopenias, and a variable degree of bone marrow involvement. There may be splenic hilar nodes in 25% of cases. The disease is often associated with hepatitis C infection, which is thought to have a tumorigenic role in some cases. Splenectomy may be performed in patients with splenomegaly for diagnostic purposes but also has a therapeutic role in the disease and is the treatment of choice. Rituximab is used in those not suitable for surgery.\textsuperscript{131}

Hairy cell leukemia (HCL) is an indolent B-cell lymphoproliferative disorder that was initially recognized by Ewald in 1923. It accounts for only 2% to 3% of adult leukemias. The typical presentation includes cytopenia, circulating hairy cells, and splenomegaly. Splenectomy was the first treatment for HCL, but highly effective chemotherapy with purine analogues now replaces splenectomy in most patients. Splenectomy is indicated for symptomatic splenomegaly, for refractory cytopenia, or as a temporizing measure in pregnancy.\textsuperscript{132} Approximately 50% of patients will have normal hematologic parameters after splenectomy, and 90% will improve in at least 1 parameter.\textsuperscript{133}

**OTHER DISEASES AND SPLENECTOMY**

Splenectomy may significantly improve the neutropenia in patients with Felty syndrome characterized by splenomegaly, neutropenia, and arthralgia. Splenectomy is reserved for patients with severe granulocytopenia ($<1 \times 10^9$/L) and recurrent infections despite antirheumatic drugs, increased
transfusion requirements, or marked thrombocytopenia. Although splenectomy does not reduce arthralgia, leg ulcers, when present, generally heal.

In patients with left-sided portal hypertension secondary to splenic vein thrombosis, splenectomy is effective to treat bleeding from gastric varices. The extensive hilar varices represent a contraindication to laparoscopic splenectomy. Indication for splenectomy is controversial in the setting of noncomplicated left-sided portal hypertension.

Splenectomy may also be indicated for symptomatic splenomegaly or severe secondary hypersplenism in patients with Gaucher disease or sarcoidosis, although splenectomy will not alter the course of the disease.

**Splenectomy**

The first recorded splenectomy was performed for splenomegaly on a 24-year-old Neapolitan woman in 1549 by Adrian Zacarelli. Over the next several centuries, however, only a few other splenectomies were attempted, most proving fatal. In a 1908 literature review of all published cases of splenectomy, totaling fewer than 50 splenectomies, surgery had a mortality rate close to 90%. Over the past 100 years, and in particular the first few decades of the 20th century, improvement in surgical techniques and a better understanding of the splenic anatomy have led to a significant reduction in surgical mortality and morbidity. By the 1970s, the mortality had been reduced to around 10%, and now most elective series report mortality rates of less than 1%.

Open splenectomy remains the standard therapy for splenic injury in trauma and emergencies, as it allows quick control of bleeding and easy assessment of other organs for injury. Although some trauma centers have reported successful management of splenic injuries laparoscopically, the laparoscopic approach is typically reserved for elective procedures.

The laparoscopic approach is now the approach of choice for almost all diseases where splenectomy is required. Benefits of the laparoscopic approach include less postoperative pain, decreased complications, shorter length of stay, faster return to full activity, and a better cosmetic result when compared with the open technique. This also extends to many patients with splenomegaly (≥15 cm length), who may benefit from a hand-
assisted laparoscopic approach with less pain and shorter hospital stay, even for cases with massive splenomegaly (≥20 cm). Although patients with malignancy and splenomegaly have a higher risk of complications compared to patients with smaller spleens, this is also the case for open splenectomy, and the laparoscopic approach is preferred when feasible.

Although many single, higher-volume institutions report rapid uptake of laparoscopic splenectomy, population data analysis suggest that the procedure is underused in the United States, with only 13% of nontrauma splenectomies performed laparoscopically and a conversion rate of 33%. Therefore, there is significant room for improvement in the uptake of this approach, but this may be hampered by the fact that outside of large referral centers, the individual surgeon will have low case volumes and limited training opportunities.

Splenectomy is performed for diagnostic purposes or for clinical indications (eg, blood cell count, abdominal discomfort) rather than for a clinical diagnosis. The clinical benefit of splenectomy should balance or outweigh the short-term and long-term risks of splenectomy.

**Preoperative Preparation and Vaccination**

The spleen contributes to the immune system by cell filtration, antibody and opsonin production, and phagocytic clearance of bacteria. Asplenic or hyposplenic patients are particularly susceptible to encapsulated bacteria, such as pneumococcus and malaria. The liver may compensate for the loss of the immunologic function of the spleen, but this requires an intact complement system and higher antibody production.

The major concern after splenectomy is overwhelming postsplenectomy infections (OPSI), defined as rapidly evolving sepsis, meningitis, or pneumonia caused by *S pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitides*, with a high mortality rate of 40% to 50%. The exact prevalence is difficult to define due to variability in follow-up, indications for splenectomy, inclusion of adults and children, and use of vaccination. Young children, particularly those younger than 2 years, are at increased risk because of the immaturity of the immune system. A review of the literature from 1966 to 1996 found a crude rate of infection of 3% with an overall mortality of 1.5%. The lowest risks were after splenectomy for ITP.
The risk persists over the patient’s lifetime, with cases reported even 20 to 30 years after splenectomy. Some of the risk is due to the underlying condition originally leading to splenectomy or to immunosuppressive therapies used to treat the condition. To account for this, an analysis of Danish splenectomized patients from 1996 to 2005 matched them to nonsplenectomized patients with the same disease. The overall incidence of infection was 7.7 per 100 person-years in splenectomized patients with the highest risk seen in the first 90 days after surgery. In this study, enteric rods were the most common cause of early and late bacteremia. The risk of infection requiring hospital care was 4.6 times higher in splenectomized patients compared to the general population. The highest risks were seen after splenectomy for underlying hematopoietic cancer, and patients with splenic trauma had the lowest risks. However, the risk was only modestly higher compared to nonsplenectomized patients with the same diagnosis; for ITP and trauma, the risk of late infections was not significantly higher than in nonsplenectomized controls. Furthermore, although mortality risk was higher compared to the general population, most of this risk was accounted for by the underlying splenectomy indication. For ITP, after 1 year, splenectomized patients had a lower mortality risk than nonsplenectomized patients.

Several strategies have been developed to reduce the risk of OPSI, and these include vaccination programs, prophylactic antibiotic use, patient education, empiric antibiotic use for febrile illness, and, importantly for the surgeon, splenic salvage whenever possible.

**VACCINATION**

Patients undergoing splenectomy or partial splenectomy should be vaccinated against encapsulated organisms with recombinant polyvalent *S. pneumoniae*, *H influenzae* type B, and *N meningitides* vaccines. Although such vaccination routine is recommended by most, there is significant international variation between recommendations regarding exact vaccine type and boosters. There are over 90 serotypes of *S. pneumoniae*, and at least 30 can cause infections in humans. The polyvalent pneumococcal vaccine (PPV-23) provides short-term immunity against 23 subtypes, and nonresponders at high risk for invasive disease can be identified by measuring antipneumococcal
antibodies. A 13-valent pneumococcal conjugate vaccine (PCV-13) is more immunogenic but has more limited serotype coverage. This is a rapidly changing field with examples of recommendations for adults summarized in Table 77-4; updates are available from the appropriate national public health bodies (web pages listed in table).

**TABLE 77-4: CURRENT GUIDELINES FOR VACCINATIONS TO PREVENT OVERWHELMING POSTSPLENECTOMY INFECTIONS**

<table>
<thead>
<tr>
<th>Website</th>
<th>At Least 2 Weeks Preoperatively</th>
<th>Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States guidelines (Centers for Disease Control and Prevention)</td>
<td>PCV13* MenACWY Hib</td>
<td>Pneumococcal  • PPV23 3 months later  • Revaccinate with PPV23 5 years later</td>
</tr>
<tr>
<td>British guidelines</td>
<td>Hib/MenC vaccine MenB PPV23</td>
<td>Meningococcal  • Booster: MenACWY 2 months later  • Revaccinate with MenACWY 5 years later</td>
</tr>
<tr>
<td>Canadian guidelines</td>
<td>PCV13 MenACWY Hib</td>
<td>Influenza  • Annual vaccine  • Measure PPV response 4-6 weeks later  • 2 doses of PCV 2 months apart for nonresponders  • Revaccinate responders at 5-year intervals or guide by titer levels  • Booster: MenACWY conjugate vaccine and MenB 1 month later</td>
</tr>
</tbody>
</table>

*If have not received PCV13 or PPV23 in the past.

These vaccines should be started at least 2 weeks before planned splenectomy and ideally when immunosuppressive agents are not used. Vaccine effectiveness may be reduced in patients who have received the anti-CD20 antibody rituximab in the previous 6 months. Guidelines for postsplenectomy vaccinations for patients who have undergone an emergency procedure suggest that waiting until 2 weeks after splenectomy results in the highest antibody titers for the most common serotypes. If there is concern that the person may not return for postsplenectomy vaccinations, vaccines should be given before discharge to improve vaccination rates, which have
been reported to be as low as 26%, even in more recent literature.\textsuperscript{151} Patients should also receive the influenza vaccine annually due to the risk of secondary bacterial infections.

**ANTIBIOTIC PROPHYLAXIS**

Recommendations for daily antibiotic prophylaxis are based on little evidence.\textsuperscript{142} Lack of compliance and risk for selection of resistant pneumococcal strains are concerns with this approach. Guidelines recommend daily prophylactic antibiotics (benzylpenicillin) for children under 5, but there is a lack of consensus on when this should be discontinued. British guidelines recommend prophylaxis until the age of 16 and suggest that lifelong prophylaxis be offered for high-risk patients (inadequate serologic response to pneumococcal vaccination, history of invasive pneumococcal disease, splenectomy for underlying hematologic malignancy, ongoing immunosuppression, age >50 or <16 years).\textsuperscript{149}

**PATIENT EDUCATION AND RESCUE ANTIBIOTICS**

Many patients are not aware of their increased risk for sepsis, and informed patients seem to have lower risks of infections.\textsuperscript{152} Patients should wear a medical alert bracelet. This is particularly important as vaccination does not imply immunity and the pneumococcal vaccine is only 70\% protective even in the immunocompetent host.\textsuperscript{147} OPSI is a medical emergency with septic shock that develops in only a few hours, and immediate treatment can reduce mortality. However, the initial prodrome of fever, myalgia, emesis, headache, and abdominal pain may go unrecognized without heightened awareness of the possibility of postsplenectomy sepsis. These early symptoms can quickly escalate into profound septic shock, accompanied by disseminated intravascular coagulation, and organ failure. Meningitis (particularly among children) and pneumonia are often seen. \textit{S. pneumoniae} is the most common cause, followed by \textit{H. influenzae} type B and \textit{N. meningitides}.\textsuperscript{142} \textit{E. coli}, \textit{Pseudomonas aeruginosa}, and other organisms can also be seen.\textsuperscript{142} Asplenic or hyposplenic patients should be instructed to seek immediate medical attention at the first sign of illness, especially fever, and immediate treatment with empiric antibiotics is mandatory. Patients should have a supply of antibiotics on hand for emergency use. With the onset of fever, the patients
should take the first dose of antibiotics and then seek immediate medical evaluation. Amoxicillin-clavulanate and levofloxacin are appropriate choices for this purpose.

OTHER RISKS OF SPLENECTOMY

In addition to OPSI, there are other short- and long-term risks of splenectomy that are taken into consideration when making clinical decisions and discussing risks and benefits with patients. These risks vary with the underlying condition but include early venous thromboembolic events, especially in the portal-splenic venous system (PSVT) (discussed below). There is concern that splenectomy may also increase the risk of late vascular events, including thromboembolism and pulmonary hypertension, especially when performed in patients with thalassemia and sickle cell disease. Splenectomy is now reserved for very rare indications in these diseases.144

SELECTION OF OPERATIVE APPROACH

Laparoscopic splenectomy was first described by several groups in 1991 and 1992.153-157 The original approach was anterior with the patient supine, as for open surgery. This was challenging, as the gastrosplenic and splenorenal ligaments lie on top of one another. The description of the lateral approach was an innovation enabling easier and safer access to the splenic hilum.158 Advances in energy devices and staplers facilitated the diffusion of the approach, eliminating the need to dissect and control the short gastric and hilar vessels individually. Finally, the addition of the hand-assisted laparoscopic technique enabled many patients with splenomegaly, even massive splenomegaly, to benefit from a less invasive procedure. The benefits of laparoscopy are predicated on the fact that an intact specimen is usually not required for pathologic diagnosis so the spleen can be removed piecemeal through the small port incisions. Even when an intact specimen is need, such as for a splenic mass, the incision will be smaller than a standard laparotomy and can be positioned lower in the abdomen.

Most patients undergoing elective splenectomy are candidates for a laparoscopic procedure. Decisions regarding the best operative approach are based on the spleen size, underlying disease, other comorbid conditions,
presence of perisplenic collaterals and inflammation, need for an intact specimen, and surgeon experience. Decisions about selection of operative approach begin with history and physical examination. The patient is examined in the supine position with arms at the sides, starting in the right lower quadrant and moving toward the left upper abdomen. Although normal splenic size varies depending on sex, age, and racial background, spleen size tends to decrease with age. While a palpable spleen up to 2 cm below the costal margin may be a normal variant in a young adult, it is likely abnormally enlarged in an older adult. A palpable spleen leads to imaging with ultrasound and/or CT scan to measure the maximal craniocaudal length of the spleen and look for other conditions that will increase technical complexity of splenectomy including perisplenic varices, splenic infarcts, and hilar lymphadenopathy.

Table 77-5 provides a general classification of spleen size that can be used for preoperative planning. Preoperative spleens that are >25 cm in length pose particular challenges laparoscopically.

<table>
<thead>
<tr>
<th>Splenic Length (cm)</th>
<th>Splenic Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal spleen</td>
<td>Up to 13</td>
</tr>
<tr>
<td>Mild splenomegaly</td>
<td>&gt;13–15</td>
</tr>
<tr>
<td>Moderate splenomegaly</td>
<td>16–20</td>
</tr>
<tr>
<td>Massive splenomegaly</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Some believe that preoperative splenic volume (rather than length alone) provides a more reliable assessment of the degree of splenic enlargement to predict difficulty of the laparoscopic approach. With improved CT technology, such volumetric assessment is increasingly easy to perform. However, until greater use and validation of these measurements are available, splenic length remains the most common measure of the degree of splenomegaly. Ultrasound splenic length measured with the patient in supine position has a good correlation with overall splenic volume on CT scan,
although measurements obtained with the patient in the right lateral decubitus position provide the strongest correlation with splenic volume.\textsuperscript{159}

**Patient Selection for Laparoscopic, Hand-Assisted Laparoscopic, or Open Approach**

Achieving the best outcomes depends on risk stratification, operative planning, and patient selection for laparoscopic, hand-assisted laparoscopic, or open surgery, based on spleen size, underlying disease, and surgeon experience. Perioperative risk increases as splenic size increases. Several studies document increased risks associated with conventional laparoscopy in the setting of splenomegaly (>1000 g). Challenges with large spleens include difficulties manipulating and moving the large organ, perisplenic adhesions and inflammation, large collateral vessels, reduced surgical space, and difficulties with extraction of the specimen. Laparoscopic splenectomy for splenomegaly has longer operative time, increased blood loss, higher risk of conversion to open splenectomy, increased postoperative length of stay, and higher postoperative morbidity when compared to splenectomy for smaller spleens.\textsuperscript{160,161} This is related both to technical issues and risk of significant bleeding, but also to the older age and underlying malignant disease in many patients with splenomegaly.\textsuperscript{162} However, significant morbidity is also seen after open splenectomy for splenomegaly,\textsuperscript{163} and the more salient comparison is between laparoscopic and open surgery for splenomegaly. In experienced hands, a laparoscopic approach is preferred over open surgery, with lower blood loss, lower or similar morbidity, and lower hospital stay,\textsuperscript{135,162,164} but it should be appreciated that splenomegaly cases are considerably more challenging than for normal-sized spleens. The introduction of the hand-assisted laparoscopic surgery (HALS) approach has improved safety for splenomegaly patients, with decreased conversions and fewer complications compared to standard laparoscopy\textsuperscript{165} and to open surgery.\textsuperscript{138} Conversion rates to open splenectomy start to increase with a spleen size of greater than 22 or 23 cm,\textsuperscript{166,167} and patients converted for complications likely suffer poorer outcomes than patients who undergo a controlled open operation.\textsuperscript{168,169}

The size cutoff above which conversion to open is inevitable based on lack of working space, inability to extract the spleen in a retrieval bag, or
conversion for complications is not clear. Some have proposed using clinical examination criteria, excluding those with spleens that extend below and to the right of the umbilicus.\textsuperscript{170} Three-dimensional CT spleen volume $>2700$ mL was associated with an 87.5\% conversion rate, with no conversions for spleens $<1100$ mL.\textsuperscript{169} In earlier studies, conversion for spleens $>25$ cm was inevitable, but more recent series report excellent results from experienced groups with liberal use of HALS for massive splenomegaly, including removal of spleens up to 35 cm long.\textsuperscript{171-173} The list of absolute contraindications to laparoscopic approach has diminished over time. Excellent outcomes even in the most challenging patients with splenomegaly in the context of cirrhosis have been reported in experienced hands.\textsuperscript{174} Splenic length $>20$ cm is a reasonable measure of anticipated difficulty, and a hand-assisted approach or open surgery for these patients is appropriate, depending on available expertise (Fig. 77-16).
Preoperative Splenic Artery Embolization

Although initial experience with total splenic artery embolization (SAE) was discouraging and associated with significant complications, partial SAE has been used to manage select cases of splenic trauma (see above). SAE has also been used by some as a preoperative intervention to reduce vascularity and size of massive spleens in preparation for a laparoscopic approach. Embolization is achieved using microcoils and/or Gelfoam.

It is generally agreed that SAE is not helpful in laparoscopic cases where the spleen measures less than 20 cm in length. The benefit of SAE in preoperative management of larger spleens remains controversial. Although some studies have shown that preoperative SAE can lead to reduced intraoperative blood loss in cases of large spleens, they reported no significant differences in conversion rates, incidence of postoperative complications, or length of hospital stay. The potential for a modest reduction in blood loss, however, needs to be balanced against the potential risks and additive nature of this procedure. Complications have been reported in up to 20% of cases and include catheter site hematoma and pseudoaneurysm, pancreatitis, splenic abscess or rupture, peritonitis, and postembolization syndrome (ie, pain, fever, ileus, and/or pleural effusion). Some of these risks can be reduced by performing surgery as soon as possible (ideally within a few hours) after embolization, but this may not be feasible in all settings. There is also a theoretical concern about stapler integrity when firing across vessels occluded by coils. In general, preoperative SAE is now infrequently used.

Laparoscopic Splenectomy

The first attempts at laparoscopic splenectomy were performed through an anterior approach. This was performed with the patient in the lithotom
position using 5 laparoscopic ports. Most now favor the lateral approach. The lateral approach, initially developed for adrenalectomy, uses the weight of the spleen and gravity to gain exposure during various steps of the procedure. In addition, it facilitates dissection of the superior short gastrics and superior pole when compared to the traditional anterior approach. A fully laparoscopic approach is chosen for spleens <15 to 20 cm in length when an intact specimen is not required, allowing for splenic morcellation and removal through a small port. Otherwise, a hand-assisted approach will be planned (see below).

**Details of the Operative Procedure: Lateral Approach**

**PATIENT POSITIONING AND ROOM SETUP**

*Figure 77-17* illustrates the room setup and patient positioning for this procedure. Monitors are placed on either side of the patient toward the head. The surgeon and assistant will stand on the right of the table with the scrub nurse on the left side. With the patient supine, an orogastric tube is placed for gastric decompression, and compression stockings are used for prevention of thrombosis. A Foley catheter is placed if the case is expected to last over 3 hours. The patient is then positioned in right lateral decubitus at about 70 degrees. The umbilicus of the patient should be at the level of where the table will be flexed. A large gel roll is placed behind the patient, and an axillary roll is placed under the right arm. The right leg is bent and the left leg is straight, with a pillow between. The table is flexed to increase the distance between the costal margin and iliac crest. The patient is taped securely to the table at the shoulders and hips. The sterile field should extend from the nipples to the pubic bone in the cranial-caudal position and from the right anterior axillary line to the left scapular tip. A formal open laparotomy set should be readily available in case emergent conversion to an open procedure is necessary. A hand-assist device should also be available as this may prevent full conversion to open surgery in some cases.
FIGURE 77-17 Patient and trocar positioning for laparoscopic splenectomy. Patient is in right lateral decubitus with table in flexion. A. Recommended trocar placement for normally sized spleen. One 12-mm port for introduction of the laparoscopic stapler. The remaining ports are 5 mm. B. Setup for hand-assisted laparoscopic splenectomy in the presence of splenomegaly. The usual hand-port placement is marked in cephalad to the umbilicus. (Reproduced with permission from Feldman LS. Laparoscopic splenectomy: standardized approach, World J Surg. 2011 Jul;35(7):1487-1495.)

TROCAR PLACEMENT

A 4-trocar technique is used, including one 12-mm port and three 5-mm ports, with a 5-mm 30-degree laparoscope for visualization. We use an open technique to insert a 12-mm port about 5 cm below the costal margin along a line drawn from the umbilicus to the costal margin. If the spleen is palpable, this trocar is moved downward to avoid splenic injury. This port will be used for the surgeon’s right hand, including stapler placement, and later for specimen retrieval. Long-acting local anesthetics are infiltrated prior to incisions. Pneumoperitoneum with carbon dioxide to a pressure of 12 mm Hg is usually adequate for exposure. The table is placed in reversed Trendelenburg position. Two 5-mm trocars are then placed under direct
vision, one to the left of the xiphoid and the next one lower down toward the midline. Lateral colonic attachments may need to be divided to place the fourth 5-mm trocar laterally below the costal margin. The camera port is placed in the most medial port to begin the dissection of the gastrosplenic ligament with the lateral port used for the assistant to provide gentle traction on the spleen (see Fig. 77-17).

**DISSECTION**

The procedure begins by exploring the abdomen to identify any accessory spleens. They are present in up to 20% of patients and may be the source for inadequate response to splenectomy in the treatment of hematologic disease, such as ITP. The rate of retrieval of accessory spleens is similar after laparoscopic and open surgery. The splenic hilum, gastrosplenic ligament, gastrocolic ligament, greater omentum, mesentery, and presacral space are potential sites for accessory spleens, with the splenic hilum being the most common (see Fig. 77-4). Each of these sites should be considered as the dissection continues.

We use an ultrasonic energy device for the dissection. It is important for the surgeon and assistants to avoid injuring the spleen, which can result in splenosis or tumor rupture. Retracting instruments are always placed with the tip past the spleen to avoid inadvertent injury (“past pointing”). The dissection begins by mobilizing the splenic flexure of the colon to provide adequate exposure to the inferior pole of the spleen (Fig. 77-18A). We begin medially with control of the short gastric vessels. With the stomach gently retracted medially by the surgeon’s left hand, and the spleen gently retracted leftward through the assistant’s lateral port, the lesser sac is entered in an avascular area near the lower pole of the spleen. Subsequently, the short gastric vessels are identified and divided using the ultrasonic dissector moving cranially. It is important to avoid any injury to the stomach or the spleen, especially cranially as the short gastrics may be very short (Fig. 77-19). Opening up the first layer of peritoneum of the gastrosplenic ligament at the top of the spleen may help to increase the length between the stomach and spleen and facilitate vessel control. Ongoing medial rotation of the stomach will help expose these vessels and ensure complete ligation (Fig. 77-18B).
FIGURE 77-18 Steps of laparoscopic splenectomy. **A.** Divide the short gastric vessels using ultrasonic dissecting shears. **B.** Medial rotation of the stomach can help visualize the superior-most vessels. Special care and attention should be given to these vessels, which are often very short in length. **C.** Dissection of the lower pole of the spleen away from the colon. **D.** The lateral attachments of the spleen are mobilized, freeing the spleen from its superior attachments and visualizing into the lesser sac from the lateral position. **E.** Divide the splenic hilum using an endoscopic stapler.
FIGURE 77-19 Care must be taken to carefully dissect the uppermost short gastrics away from the stomach. These may be very short.

Once all the short gastrics are ligated, the lower pole of the spleen is elevated with a blunt dissector and any attachments are divided (Fig. 77-18C). Once the inferior pole of the spleen has been freed, attention is turned to the lateral splenic attachments (Fig. 77-18D). The scope is moved to the lateral port to improve exposure. The surgeon’s nondominant hand provides gentle traction rightward on the spleen to expose the lateral attachments. These are divided moving caudal to cranial and staying 5 to 10 mm away from the spleen. At the upper pole, the spleen is retracted upward in order to place the posterior gastroplenic peritoneal layer on stretch and reenter the lesser sac laterally. It is important to ensure complete mobilization superiorly in order to facilitate hilar control.

Once the spleen is fully mobilized, the position of the pancreas in relation to the hilum is assessed. The pancreas is usually within 1 cm of the hilum. If there does not appear to be sufficient space for a stapling device between the spleen and pancreas, additional fine division of tissue in this area can be achieved using hook dissection. The hilum is divided with an endoscopic stapling device (Fig. 77-18E). The hilum should be divided close to the spleen to avoid injury to the pancreatic tail. Depending on the spread between the hilar vessels, a $60 \times 2.5$-mm stapler or $45 \times 2.5$-mm stapler is chosen and
articulated to achieve precise application across the hilum. The splenic bed and short gastrics are inspected for hemostasis. Occasionally, oozing from the staple line may require application of a metal clip or suture.

REMOVAL OF THE SPECIMEN

The 12-mm port is removed and the incision extended to enable a 15-mm endoscopic bag to be placed directly through the skin incision without a port. The spleen is placed in the endoscopic bag, and the bag is brought up through the skin. The spleen is then morcellized using a ring forceps and digital disruption and the pieces removed or suctioned until the entire bag can be removed from the abdominal cavity. Care should be taken during this part of the procedure to ensure that the ring forceps do not tear the retrieval bag causing splenosis or inadvertent grasping of intra-abdominal contents through the bottom of the bag. This can lead to unrecognized complications, such as small bowel or colonic injury. The 12-mm port is then replaced and pneumoperitoneum reinstilled in order to verify hemostasis and exclude any injury to the pancreas, diaphragm, or stomach. Adjuncts for controlling any oozing along the staple line may include application of fibrin sealant. In patients with ITP and low platelets who are oozing after hilar division, platelet transfusion is given.

The fascia of the extraction port is closed with slowly absorbable suture and the skin approximated with absorbable sutures. The orogastric tube is removed in the operating room and the urinary catheter is also removed, unless there was significant blood loss and need for ongoing close monitoring. We do not leave a closed suction drain unless there was concern of injury to the pancreatic tail. If a drain is placed, the drain fluid amylase and lipase are assessed after the patient starts on an oral diet, and if normal, the drain is removed. If the patient has evidence of a pancreatic leak, the patient is discharged with the drain left in place until output is less than 10 mL for 2 days.

Considerations for Splenomegaly

Cases of massive splenomegaly (≥20 cm length) are technically challenging, and the risk of complications and conversion is higher than for smaller
spleens, requiring some adjustments in strategy. The HALS technique is useful because it facilitates exposure and manipulation of the very large and heavy specimen in order to better access the splenic attachments, especially laterally and superiorly. Another advantage is that the placement of the large specimen in a bag for retrieval can be extremely difficult using small laparoscopic instruments. HALS increases safety significantly, with the ability for the hand to control the hilum in the case of bleeding, decreasing blood loss and avoiding conversion to open surgery\textsuperscript{180} while maintaining the advantages of the laparoscopic approach.\textsuperscript{138,162}

The planned 7- to 8-cm incision for the hand port is marked in the midline prior to positioning the patient and is for the surgeon’s nondominant hand (Fig. 77-18B). Although variable positions for the port have been described, we place it in the supraumbilical midline, immediately cephalad to the umbilicus. A number of such ports are commercially available.

The patient is placed in right lateral decubitus but at less of an angle than for a smaller sized spleen to facilitate medial access to the lesser sac for early vascular control and conversion to open surgery if needed. The spleen edges are marked after positioning the patient, and initial port placement will be below the level of the palpable spleen to avoid injury. We prefer to begin the dissection laparoscopically because insertion of the hand will obscure the view somewhat. Attention should be paid to the presence of larger blood vessels, including to the lower pole and potentially vascularization of the usually avascular perisplenic attachments. The lesser sac is entered, and short gastrics are divided. With very large spleens, the splenic artery is identified proximal to the hilum, dissected, and controlled with a self-locking clip, suture, or TA stapler, without dividing the vessel (Fig. 77-20). The hand may be inserted at this point to facilitate identification and control of the splenic artery. Early ligation of the splenic artery decreases blood flow and splenic volume and provides some reassurance to the surgical team. If a clip is used, care is taken to ensure it is proximal to where the hilum will be stapled later to avoid misfiring.
In cases with significant splenomegaly, the splenic artery is identified after opening the lesser sac and ligated prior to additional splenic mobilization.

In cases of massive splenomegaly, the lower pole attachments may contain sizable vessels that may require clips, ties, or stapling. Lateral splenic mobilization is greatly facilitated by the hand providing retraction rightward and downward as the upper pole is approached (Fig. 77-21). Similarly, stapler placement across the hilum in very large spleens is much easier and safer with HALS. Once the spleen is detached, placement of the spleen inside the specimen bags can be very challenging. For spleens greater than approximately 20 cm, we pull a large “bowel bag” over the spleen placed in the left upper quadrant with the patient in a head-down position.
FIGURE 77-21 The hand can be useful in providing medial traction to expose the superior lateral attachments in cases of splenomegaly.

When there is significant perisplenic inflammation, there may be ongoing oozing from the wide dissection field. Applying hemostatic adjuncts like fibrin sealants using the spray applicator can be effective, as can sheets of absorbable oxidized cellulose.

Postoperative Management

Traditionally surgeons have advocated postoperative decompression of the stomach with a nasogastric tube to prevent hemorrhage from the short gastrics. This is not necessary after uncomplicated splenectomy. Patients are given clear liquids on the night of surgery, advancing the diet the next morning. A single dose of preoperative antibiotics is used and is not repeated postoperatively. Perioperative thromboprophylaxis with subcutaneous heparin is used. The patients are provided patient-controlled analgesia for their first postoperative night and switched to oral analgesia in the morning. Unless the patient has an ongoing coagulation problem or low platelet counts, we use nonsteroidal anti-inflammatory drugs in management of their
postoperative pain. A complete blood count is checked the morning after surgery. Patients are typically discharged on postoperative day 1 or 2 after laparoscopic splenectomy and day 2 or 3 after HALS.

**Complications**

Overall, the complication rate of elective laparoscopic splenectomy is 10% to 15%, with a mortality rate of less than 1%. Splenectomy for hematologic malignancy and splenomegaly has a higher complication rate, with reports of a 9% to 18% mortality rate for patients with myeloproliferative disorders.\(^{124,162,181}\) In observational studies, the rate of complications was lower for patients having laparoscopic compared to open splenectomy,\(^ {135,182}\) including for splenomegaly.\(^ {135}\)

Patients must be closely monitored for early postoperative bleeding, particularly those with thrombocytopenia or myeloproliferative disorders. Patients with massive splenomegaly and underlying coagulopathy should be in a monitored setting in the immediate postoperative period. It is an error to ascribe bleeding to hematologic abnormalities, and although these should be corrected, it is generally safer to reexplore patients early and to evacuate a hematoma to reduce the incidence of subphrenic abscess.

Injury to the tail of the pancreas with a symptomatic complication can occur in up to 10% of cases.\(^ {183}\) Development of a pancreatic collection will require drainage that remains in place until the fistula closes. Pulmonary complications such as atelectasis, effusion, and pneumonia occur more frequently following open splenectomy. One intraoperative complication that may occur during laparoscopic splenectomy but is rarely seen with open splenectomy is diaphragmatic perforation, usually related to thermal injury during mobilization of the superior pole, emphasizing the importance of a good technique and visualization during the procedure.\(^ {168}\)

In unusual cases, the platelet count may rise to very high levels. In cases where the platelet count rises to \(>1000 \times 10^9/L\), a drug that inhibits platelet aggregation, such as acetylsalicylic acid, can be used.

Thrombosis of the splenic vein, with extension into the portal vein and superior mesenteric vein, is a potentially lethal complication of splenectomy if it results in bowel ischemia or portal hypertension. A range of estimates for this complication (0% to 55%) has been reported due to variations in study...
design, such as whether retrospective or prospective, indication for splenectomy, surgical approach, and method of diagnosis (with CT scan twice as sensitive as ultrasound). In a review of splenic-portal vein thrombosis (SPVT), the overall incidence of symptomatic thrombosis was 3.3% and similar between the open and laparoscopic approach. However, when considering only prospective studies that screen for asymptomatic cases, the overall incidence increased to 12.3% and was significantly higher after laparoscopic compared to open surgery (23% vs 8%) (Fig. 77-22). Patients with myeloproliferative disorders, lymphoproliferative disorders, and hereditary hemolytic anemias (particularly HS and thalassemia) are at particularly high risk, whereas patients with ITP are at lower risk.

Interestingly, splenectomy for trauma is not associated with a significant risk for SPVT. Clinically, patients with splenomegaly are at higher risk than patients with smaller spleens. In one study, the incidence of SPVT on screening postoperative Doppler ultrasound was 78% for patients with spleen size >20 cm, 31% for spleens between 15 and 20 cm, and 13% for spleens ≤15 cm. Although abnormalities in prothrombotic screening tests are very common, they do not predict SPVT.
FIGURE 77-22 Splenic-portal vein thrombosis (SPVT) after a laparoscopic splenectomy. The thrombosis may be small and involve intrahepatic branches of the portal vein only, as is the case here where the patient had thrombus in the anterior branch of the right portal vein. The patient was asymptomatic and was initially observed. Follow-up imaging after 3 weeks, however, showed persistent thrombosis, and she was therefore anticoagulated for 3 months.

The high incidence of asymptomatic SPVT has generated a debate about whether patients should have surveillance imaging (ultrasound or CT) after laparoscopic splenectomy, since untreated thrombosis could lead to significant morbidity and mortality. The median time from splenectomy to asymptomatic SPVT is 6 days, whereas the median interval to symptomatic SPVT is about 8 to 12 days. Prompt treatment of asymptomatic PSVT leads to resolution in 90% of cases, but it is also known that isolated thrombosis in the splenic vein may resolve without anticoagulation. However, persistent thrombosis, portal hypertension, or cavernoma is present in 20% of patients after treatment of symptomatic SPVT. Some advocate screening all patients with Doppler ultrasonography 1 to 3 weeks after laparoscopic splenectomy, whereas others suggest screening only higher risk patients. We perform routine postoperative surveillance ultrasound with color Doppler imaging on postoperative day 7 and anticoagulate patients for 3 to 6 months if SPVT is detected. Since symptoms of SPVT can be subtle, abdominal imaging should be performed for any patient with any deviation from the expected postoperative course, including fever, abdominal pain, diarrhea, anorexia, or nausea.

Perioperative anticoagulation prophylaxis is recommended, and European Association for Endoscopic Surgery guidelines further recommend prophylactic anticoagulation for 4 weeks after surgery. Although a single small randomized trial of extending postoperative prophylaxis failed to show a benefit, this is strongly considered for patients at particularly high risk (eg, myelodysplastic disorders with splenomegaly) once hemostasis is assured.

OPEN SPLENECTOMY

The open approach is most commonly used in cases of trauma and splenic
injury, but it is also used in elective management of massive splenomegaly (Fig. 77-23).
FIGURE 77-23  A. This spleen measured 27 cm and was successfully removed laparoscopically. B. This spleen measured over 30 cm and was removed through open surgery.

The patient is supine, with an optional small roll under the left flank. A variety of incisions including left subcostal or midline can be used depending on the nature of the disease and the personal preference of the surgeon. A midline incision is used for traumatic injury because of the speed of access as well as exposure of the spleen and other possibly injured viscera. A careful look for accessory spleens is made in hematologic disease around the splenic hilum, retroperitoneum around the pancreatic tail, and greater omentum.

Open splenectomy is performed by mobilizing the spleen medially and ultimately dissecting down to a pedicle of splenic artery and vein, which is then controlled and divided. The surgeon stands on the right side of the table. A self-retaining retractor is used to expose the left upper quadrant and retract the colon downward. The gastrosplenic omentum is opened in an avascular area, and the short gastric vessels are divided with clips, sutures, or an energy device, taking care to avoid injury to the stomach (Fig. 77-24). The most difficult area is high on the stomach where the vessels are shortest and the risk for bleeding and gastric injury are highest. If there is concern about the gastric wall, a seromuscular suture is placed on the stomach to invert the area of concern. In cases of massive splenomegaly, the splenic artery can be isolated and ligated after the short gastrics are divided. Alternatively, the splenic artery can be identified nearer to its origin, avoiding the splenic vein and tail of the pancreas, through the gastrohepatic ligament along the lesser curve of the stomach (Fig. 77-25)
FIGURE 77-24  Ligation of the short gastric vessels and the gastroplenic omentum.
FIGURE 77-25 In cases of massive splenomegaly, access is obtained to the lesser sac and the splenic vessels identified. The artery is often seen above the pancreas. The vessels are carefully dissected and ligated twice proximally and once distally before being divided. The splenic dissection and mobilization are then performed.

Spleenic mobilization then proceeds around the inferior pole, and the splenocolic attachments are taken down, staying close to the spleen to avoid injury to the colon or going too deep and injuring the adrenal gland. The left gastroepiploic artery is usually encountered here and controlled. The surgeon’s left hand then palpates along the surface of the spleen and progressively retracts the spleen medially, exposing the lateral attachments (Fig. 77-26). These can be divided with scissors or electrosurgery staying close to the spleen. In the case of trauma, the hematoma has usually dissected these ligaments, and the spleen can quickly be delivered into the incision.
FIGURE 77-26 Divison of the ligamentous attachments of the spleen during open splenectomy.

The spleen can then be delivered into the wound after bluntly dissecting any retroperitoneal attachments. Laparotomy pads are placed posteriorly to elevate the spleen. Hilar dissection proceeds close to the spleen to separate the vessels from the pancreas. The splenic artery and vein are individually divided between clamps and doubly ligated proximally with suture ligature (Fig. 77-27). Alternatively, the vessels may be divided with a vascular linear stapler. This is a fast way to control the hilum in cases of bleeding.
After the spleen is removed, hemostasis is checked in 3 areas: on the diaphragmatic surface, along the greater curve of the stomach, and in the hilum. In cases of splenomegaly or infarction when there is significant perisplenitis, there may be a large raw oozing surface along the diaphragm. Packs are placed in the left upper quadrant along the diaphragm, and the greater curve and hilum are examined. The packs are then removed, and if there is still oozing, fibrin glue spray along with oxidized cellulose usually is effective. Prophylactic drainage is not used unless the pancreas has been injured.

**SPLEEN-PRESERVING APPROACHES**

The techniques to preserve splenic tissue and function are dictated by the extent of planned resection or, in case of trauma, splenic damage (Fig. 77-28). These approaches have garnered increased popularity because of the critical role of the spleen in fighting encapsulated organisms and the small, but real, risk of OPSI.
Approaches to preserving a traumatized spleen. Depending on the degree of splenic injury, one of these techniques can be used.

**Splenorrhaphy**

In hemodynamically stable patients with splenic trauma or iatrogenic injury, splenic repair may be attempted. In trauma, this situation is now relatively rare as many hemodynamically stable patients undergo splenic angioembolization. The spleen is mobilized to allow for thorough inspection of the organ. The ligamentous attachments must be divided as in splenectomy. Small lacerations can be managed by compression and the application of a hemostatic agent, such as oxidized cellulose, micronized collagen, thrombin, or fibrin glue. If the injury is localized to 1 pole of the spleen, the distal branches to that pole can be ligated near the hilum via the lesser sac, followed by reapplication of hemostatic agents and pressure. If this is not successful, a plegetted repair using horizontal mattress sutures that...
traverse the capsule and incorporate the injured parenchyma can be attempted. Finally, partial splenectomy can be considered, as described below. There is no tolerance for significant blood loss during attempted splenic salvage, and splenectomy should be performed if significant bleeding cannot be quickly controlled.

**Partial Splenectomy**

Partial splenectomy is an attractive option to remove splenic lesions while preserving splenic function, which should decrease the long-term risk of sepsis and thrombosis. The indications include nonparasitic cysts, benign solid masses, Gaucher disease, and hematologic conditions such as HS or thalassemia. Recommendations about the amount of remnant splenic tissue required for normal immunity vary from 10% to 25% of the normal spleen size. Some authors suggest a splenopexy of the remnant to the retroperitoneum, abdominal wall, or gastric wall to prevent torsion. Because there is no specific information about whether patients having spleen-conserving therapy require vaccinations, the same preparation as for total splenectomy is recommended.

Whether open or laparoscopic, the key to partial splenectomy is understanding the vascular anatomy. The spleen consists of 4 to 5 segments, each with its own terminal blood supply. The interlobar planes are relatively avascular, so resection of the segmentally devascularized spleen can be performed without significant blood loss. The inferior pole is supplied by the left gastroepiploic artery and the superior pole by the short gastrics; these vessels lie in the gastrosplenic ligament. In addition, there are 2 to 3 hilar branches lying with the tail of the pancreas in the splenorenal ligament (Fig. 77-6). Balaphas et al suggest the classification of partial splenectomy shown in Figure 77-29 and Table 77-6.
FIGURE 77-29  Classification of types of partial splenectomy (see Table 77-6).
CT scan is used to plan the procedure, defining the vascular anatomy, the relationship to the lesions, and which splenic segments will be removed. Lesions in the poles of the spleen are most amenable, whereas centrally located lesions, unless an upper pole or lower pole segment can be preserved, will require total splenectomy. When partial splenectomy is performed for hereditary hemolytic anemias in children, the blood supply to the remnant spleen is maintained either through the upper short gastrics or inferior branches of the splenic artery and gastroepiploics to the lower pole, leaving about 15% to 25% of the splenic volume.\textsuperscript{190}

### Laparoscopic Partial Splenectomy

This procedure was first reported by Poulin et al\textsuperscript{191,192} in 1995, with a recent review identifying 187 cases.\textsuperscript{52} The patient is positioned as per total splenectomy and 4 ports are used. The lesser sac is entered in an avascular area, preserving the uppermost short gastrics and the gastroepiploics at this point. The hilar vascular anatomy is examined. Laparoscopic ultrasound can be used to confirm the position of the pathology if it is not evident grossly. The spleen is partially mobilized laterally, except around the area of the spleen to be preserved. The branches to the segment to be removed are serially dissected at the level of the hilum anteriorly and controlled with clips, staplers, ligature, or a vessel-sealing energy device. As the arterial blood supply is divided, the splenic parenchyma will demarcate. The corresponding venous branches lie immediately posterior to the arteries, and care must be taken not to cause bleeding. It is confirmed that the partial resection will be

<table>
<thead>
<tr>
<th>Technique</th>
<th>Segment of Spleen That Remains</th>
<th>Remaining Segment Supplied By:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Upper half of spleen</td>
<td>Upper hilar vessels</td>
</tr>
<tr>
<td>A2</td>
<td>Lower half of spleen</td>
<td>Lower hilar vessels</td>
</tr>
<tr>
<td>B</td>
<td>Upper pole of spleen</td>
<td>Short gastrics (2-3)</td>
</tr>
<tr>
<td>C</td>
<td>Lower pole of spleen</td>
<td>Left gastroepiploic</td>
</tr>
</tbody>
</table>

adequate to remove the pathology fully; if not, further branches are taken, or total splenectomy is performed. The venous branches to the devitalized segment are then divided either from the front or the back. To divide the capsule with minimal bleeding, it is first scored circumferentially with an electrosurgical device ≥5 mm on the devascularized side of the demarcation line. The devascularized parenchyma is then divided with an energy device with little bleeding. Fulguration is used to control surface oozing. Fibrin glue spray and oxidized cellulose are applied to the cut surface if necessary, and the specimen is removed in a bag.

Complications are relatively infrequent but include ischemia of the splenic remnant. Sonography and/or technetium-99m scanning are done to confirm perfusion.\textsuperscript{10} Retained splenic phagocytic function is verified by absence of Howell-Jolly bodies on peripheral blood smear postoperatively.\textsuperscript{84}

**Laparoscopic Unroofing of Nonparasitic Splenic Cyst**

The positioning is the same as for laparoscopic splenectomy, and 3 or 4 trocars are used. The cyst is aspirated by introduction of the suction device through a thin area of the wall. The spleen is mobilized to gain access to the entire diameter of the cyst. In cases where there has been leakage or rupture, significant perisplenic adhesions are seen and care must be taken to avoid injury to the diaphragm when these are divided. The anterior cyst wall is opened at the level of the splenic parenchyma and circumferentially excised using an energy device, removing as much of the wall as possible. Significant calcifications in the wall of the cyst seen on preoperative imaging may preclude unroofing, and formal cystectomy or partial splenectomy may be required. The wall is removed in a retrieval bag. Hemostasis along the cut edge is obtained and omentum is sutured to the trabeculations seen on the back wall of the cyst through the empty cyst cavity.

**REFERENCES**


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UptoDate; 2016.


ADRENAL ANATOMY AND PHYSIOLOGY

David Harris • Daniel Ruan

ANATOMY

The adrenal glands are paired retroperitoneal organs superomedial to the kidneys at the level of the 12th rib. They are surrounded by loosely attached fat posteriorly to diaphragmatic muscle. This fat can obscure the visualization and identification of adrenal tumors. Left-sided adrenal tumors lie adjacent to and can invade the spleen, pancreas tail, liver, kidney, or renal hilum. If not careful, it is possible to mistake the tail of the pancreas for the left adrenal gland given the similar texture and size. Right-sided adrenal tumors lie adjacent to and can invade the liver or inferior vena cava (IVC).

The arterial supply to the adrenals originates from the inferior phrenic arteries, aorta, and renal arteries. Despite being quite variable, the majority of the arterial supply approaches from the medial and inferior borders of the adrenals with few substantial arteries from the superior, posterior, or lateral sides. The adrenal arteries are generally small and amenable to electrocautery or vessel sealing devices.

Generally, the venous drainage from the right adrenal was thought to
consist of a single, large, short vein draining into the IVC. On the left, drainage was thought to proceed to the left renal vein or inferior phrenic vein via a longer, single vein. These anatomic descriptions were based largely on cadaveric studies on non-diseased adrenal glands. In the 1940s, Anson and Caudwell identified only a single venous variant in nearly 900 adrenals examined.\textsuperscript{1} However, others have found significant heterogeneity in venous anatomy during operative intervention for adrenal pathology. Scholten et al. found 13\% variance in venous anatomy in 546 consecutive adrenalectomies — no main adrenal vein, a single main vein with multiple small veins, double adrenal veins, and drainage sites including the IVC, hepatic vein, or inferior phrenic vein. The incidence of variant anatomy was more likely on the right side, with larger tumors, and with pheochromocytomas. Further, variant anatomy is associated with higher rates of transfusions due to operative complications.\textsuperscript{2}

**PHYSIOLOGY**

Each gland is divided into an outer cortex and an inner medulla, which are histologically and functionally distinct layers derived from separate embryologic origin. The cortex originates from mesodermal cells that form into cords of endocrine cells. In the adult, the cortex is composed of three zones. From outermost to innermost, they are: (1) \textit{zona glomerulosa}, which regulates electrolyte homeostasis via production of aldosterone in response to the renin-angiotensin system, potassium concentration, and atrial natriuretic peptide, (2) \textit{zona fasciculata}, which produces cortisol to promote gluconeogenesis and delivery of glucose to tissues, and (3) \textit{zona reticularis}, which develops after roughly age 5 and produces the androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) in response to adrenocorticotrophic hormone (ACTH) stimulation.\textsuperscript{3}

The medulla is derived from neural crest cells, called chromaffin cells, which migrate and become imbedded into the inner portion of the gland. They develop into modified postganglionic sympathetic neurons that secrete up to 80\% of the epinephrine and 20\% of the norepinephrine in circulation in response to centrally mediated sympathetic cholinergic stimuli during stress. Cortisol produced in the cortex is shuttled past the medullary chromaffin cells, which increases production of phenylethanolamine-\textit{N}-methyltransferase
(PNMT), which converts norepinephrine to epinephrine.  

**OPERATIVE ADRENAL DISEASE**

The following sections detail specific conditions along with the evaluation and treatment approaches for adrenal disease. This is summarized in Table 81-1.

**Diseases of the Cortex**

**ADENOMA**

**Cortisol Producing—Cushing Syndrome.** Adrenal adenomas that produce cortisol can be incidentally discovered during abdominal imaging or when the patient develops the signs and symptoms of Cushing syndrome. In the early 1930s, Harvey Cushing was among the first to describe the clinical entity of hypercortisolism, which is characterized by truncal obesity, round face, fragile skin, depression, and abdominal striae. These tumors autonomously secrete cortisol without the usual dependence on ACTH and can increase the risk of cardiovascular complications and mortality. Preoperative testing includes overnight dexamethasone suppression test, 24-hour urine collection for free cortisol, and salivary cortisol measurement. To perform the overnight dexamethasone test, give 1 mg of dexamethasone at 11 pm and then check serum cortisol at 8 am, which should suppress under 5 μg/dL. Some clinicians will increase the dose of dexamethasone to 2 or 3 mg, perform a 48-hour suppression test, or decrease the threshold of an abnormal am serum cortisol level to 1.8 μg/dL in order to reduce the false negative rate. Table 78-2 shows common methods for testing.

**TABLE 78-1: OPERATIVE ADRENAL DISEASE**
### TABLE 78-2: TESTING FOR ADRENAL PATHOLOGY

<table>
<thead>
<tr>
<th>Disease of the cortex</th>
<th>Phentype</th>
<th>Pre-op Test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma--Cortisol</td>
<td>Truncal obesity</td>
<td>CT/MRI</td>
<td>Lap adrenalectomy</td>
</tr>
<tr>
<td></td>
<td>Round face</td>
<td>Overnight dexamethasone suppression</td>
<td>Possible bilateral adrenalectomy</td>
</tr>
<tr>
<td></td>
<td>Fragile skin</td>
<td>24-hr urine collection</td>
<td>Post-op steroid taper</td>
</tr>
<tr>
<td></td>
<td>Striae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma--Aldosterone</td>
<td>Hypertension</td>
<td>CT/MRI</td>
<td>Lap adrenalectomy</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Plasma aldosterone:Renin ratio</td>
<td>Partial adrenalectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salt loading</td>
<td>Hold antihypertensives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selective venous sampling</td>
<td>immediately post-op</td>
</tr>
<tr>
<td>Adrenocortical Carcinoma</td>
<td>Maybe functional</td>
<td>CT/MRI</td>
<td>EDP-Mitotane</td>
</tr>
<tr>
<td></td>
<td>Compressive symptoms</td>
<td>PET-CT, 123I imaging</td>
<td>Open adrenalectomy</td>
</tr>
<tr>
<td>Disease of the medulla</td>
<td>Pheochromocytoma</td>
<td>Episodic headaches, palpitations, diaphoresis</td>
<td>Alpha-blockade + salt load</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT/MRI</td>
<td>Lap adrenalectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-hr urine metanephrines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma metanephrines</td>
<td></td>
</tr>
<tr>
<td>Extra Adrenal</td>
<td>Metastasis</td>
<td>Compressive symptoms</td>
<td>Lap adrenalectomy</td>
</tr>
<tr>
<td></td>
<td>Schwannoma</td>
<td>Non-functional</td>
<td>Surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compressive symptoms</td>
<td>Removal if symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Core needle biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraganglioma</td>
<td>Like Pheo</td>
<td>CT/MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-functional</td>
<td>Alpha-blockade + salt load</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-hr urine metanephrines</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 78-2: TESTING FOR ADRENAL PATHOLOGY

<table>
<thead>
<tr>
<th>Test</th>
<th>Protocol</th>
<th>Pathologic results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisol-adenomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Dexamethasone Suppression Test</td>
<td>Overnight low dose: 1 mg @11PM &amp; check AM serum cortisol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overnight high dose: 3 mg @11PM and check AM serum cortisol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Some clinicians use to reduce false negative rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Day test: 0.5 μg q6hrs x 8 doses and measure serum cortisol 2 to 6 hours after the last dose</td>
</tr>
<tr>
<td>Confirmatory</td>
<td>Urine* Cortisol</td>
<td>24-hr urine collection</td>
</tr>
<tr>
<td><strong>Aldosteronomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Aldosterone:Renin ratio</td>
<td>8 am plasma aldosterone and renin. For a quality test, the patient cannot be on spironolactone, eplerenone, or amiloride. It is okay to continue beta blockade.</td>
</tr>
<tr>
<td>Confirmatory</td>
<td>Salt Loading</td>
<td>Assess plasma aldosterone concentration after administration of 2 L normal saline over 4 hr while in a recumbent position</td>
</tr>
<tr>
<td><strong>Pheochromocytomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Urine* Metanephrines</td>
<td>24-hr urine collection and test for fractionated metanephrines and catecholamines.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Serum Metanephrines</td>
<td>Only to be performed if the patient has high pretest probability due to high false positive rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For urine test, creatinine should be checked to ensure adequate collection.

Adrenalectomy in this population has been associated with normalization of blood pressure, dyslipidemia, glucose metabolism, body mass index, and
improved quality of life. Bilateral adrenalectomy is indicated for severe ACTH-independent and ACTH-dependent Cushing syndrome that cannot be medically controlled. Because adrenocortical carcinomas (ACCs) also frequently secrete cortisol, a careful preoperative evaluation should be performed to look for signs of malignancy, such as radiographic evidence of local invasion, regional lymphadenopathy, distant metastases, and rapid growth. Small tumor size and well-defined borders are features commonly found in benign, cortisol-producing adenomas. Furthermore, adenomas tend to be homogenous, lack necrosis, and have radiodensities lower than 10 Hounsfield units. For newly discovered adrenal masses, the risk of ACC is significantly higher in tumors that are larger than 6 cm. When previous studies are available, comparison should be used to determine tumor growth, since ACCs tend to grow at a much higher rate than benign adenomas.

The obesity resulting from Cushing syndrome can present an additional technical challenge for laparoscopy. Furthermore, tissues tend to be weak such that port sites at the skin typically dilate during the procedure, resulting in gas leakage during the operation. Therefore, it is ideal to make the port site incisions as small as technically possible to avoid gas leakage during peritoneal insufflation.

Postoperatively, adrenal function may be suppressed in the contralateral gland, and patients should be given a prophylactic hydrocortisone taper to avoid potential postoperative adrenal insufficiency, which can be life threatening. The steroid taper can progress according to patient symptoms and can be monitored with serum cortisol and morning ACTH levels as well as an ACTH stimulation test. Clinicians should closely monitor for the signs of Addisonian crisis, which include hemodynamic instability, abdominal discomfort, fatigue, and electrolyte imbalance. Mineralocorticoid replacement with a fludrocortisone taper may also be required. Lastly, patients with mild or subclinical Cushing syndrome may not require a steroid taper. Some groups will check a serum cortisol level the morning after surgery; if levels exceed a threshold (eg, 8 μg/dL), patients can be followed closely for signs and symptoms of Addisonian crisis without a steroid taper.

**Aldosterone Producing—Conn Syndrome.** *Aldosteronomas* are cortical adrenal tumors that autonomously secrete aldosterone. Hyperaldosteronism was first described by Jerome Conn in 1955 and is characterized by
hypertension and hypokalemia. These symptoms should be controlled preoperatively with an aldosterone antagonist and potassium supplements. Biochemical confirmation of autonomous hypersecretion of aldosterone should be confirmed prior to adrenalectomy. Primary preoperative testing includes measurement of the plasma aldosterone and renin concentration where an aldosterone to renin ratio greater than 20 ng/dL or an aldosterone level greater than 15 ng/dL is indicative of disease. Confirmatory testing is best achieved by salt loading with normal saline solution and measurement of plasma aldosterone (Table 78-2). Aldosterone antagonists should be held prior to testing for at least a few weeks. While there are several forms of primary hyperaldosteronism, surgery is indicated only in the setting of unilateral adrenal adenoma or hyperplasia. There is a general lack of randomized controlled trials comparing medical and surgical management of aldosteronomas in terms of managing hypertension and albuminuria. Surgery appears to be associated with need for fewer antihypertensives, less cost (due to decreased need for intense follow-up), and overall increased quality of life.

Since benign, nonfunctional adrenal tumors are common relative to the incidence of Conn syndrome, selective venous sampling should be used to confirm laterality of disease in patients who are older than 40 years. Although many surgeons believe that computerized tomography (CT) or magnetic resonance imaging (MRI) is sufficient when unilateral disease is identified in younger patients, it is our practice to perform selective venous sampling for all patients who are considered candidates for adrenalectomy. This is supported by a recent study that found that 50% of patients within a primary hyperaldosteronoma cohort would have been inappropriately managed based on preoperative CT findings alone.

Postoperatively, normalization of aldosterone levels confirms surgical cure and is typically associated with correction of hypokalemia. Infrequently, hyperkalemia can result from chronic suppression of the contralateral adrenal gland. With complete resection of the aldosteronoma, nearly all patients have normal serum potassium levels and hypertension is improved in most. Approximately half of patients can stop all hypertensive medications after adrenalectomy, and the remainder require less medication. Thus, antihypertensive medications should be held for the first day after surgery to determine if the patient has persistent hypertension. When hypertension
persists after curative adrenalectomy, it is usually due to underlying essential hypertension.

**ADRENOCORTICAL CARCINOMA**

ACC is a rare (1-2 cases per million individuals) and aggressive tumor derived from the adrenal cortex. Women are affected more frequently than men, and left-sided tumors are more common than right. The side predominance may be related to the proximity of right-sided tumors to the IVC, thus precluding surgery and national registration. Early age at diagnosis, a family history of cancer, and parallel primary tumors in a proband should raise suspicion of an inherited cancer syndrome such as Beckwith-Wiedemann, Li-Fraumeni, Carney, multiple endocrine neoplasia 1, or Lynch syndrome.\(^{18,19}\)

At presentation, most tumors are large, and as many as 60% in adults autonomously hypersecrete cortisol or sex steroids. Preoperative findings consistent with ACC, and thus important for planning, are large size, irregular borders, and extension into surrounding structures. ACC tends to be vascular, greater than 10 Hounsfield units, and associated with necrosis on CT imaging.\(^4\) Sturgeon et al. found that tumors greater than 4 cm in size and those that were greater than 8 cm had a 10% and 47% likelihood of malignancy, respectively.\(^{20}\) Other methods such as PET-CT, mass spectrometry analysis of urinary steroid profiling, and \(^{123}\)I imaging have shown utility in the diagnosis of ACC.\(^{18}\)

The overall 5-year survival is roughly 30%. For tumors less than 5 cm and without lymph node involvement, median survival may be as high as 10 years.\(^{18}\) Metastatic disease holds a grim prognosis and is predominately dealt with medically. We recommend surgical intervention if (1) complete resection of the primary tumor is feasible in the absence of metastases, (2) when resection or ablation of oligometastases is feasible, or (3) when the patient may benefit from the palliative debulking of a functional tumor.\(^{19}\)

The cornerstone of systemic medical therapy is mitotane, which specifically targets the adrenal gland. However, mitotane is adrenolytic and it rarely results in a complete response. Other agents such as cisplatin and streptozosin are often used in concert.\(^{19,21}\) Although there was no effect on overall survival, the FIRM-ACT trial showed that use of etoposide,
doxorubicin, and cisplatin in combination with mitotane, as opposed to streptozosin, was associated with increased progression-free survival and tumor response rate.\textsuperscript{21}

Complete surgical resection is the only curative treatment for ACC. Classically, a formal lymph node dissection has not been carried out, but recent data suggest a prognostic benefit to lymph node dissection, a decreased risk of local recurrence, and a decrease in disease-related death when lymph node dissection is performed.\textsuperscript{18}

Local invasion typically precludes complete extirpation. Thus, often a large incision is necessary for adequate exposure, complete resection of invaded structures, and vascular control. All structures with evidence of invasion require resection. In a study of 133 patients who underwent open anterior resection of their ACC, 55 had an extended operation consisting of removal of the kidney (27), kidney plus other (19), or other organ (9) at their index operation. Initial recurrence at 28 months occurred most often locally, followed by distant metastasis, nodal disease, and peritoneal carcinomatosis. Median disease-free survival was 13 months, and overall median life expectancy was 43 months.\textsuperscript{22}

Patients with borderline resectable disease—as defined by imaging suggestive of resectable metastasis or local invasion requiring multiorgan or vascular resection—may benefit from neoadjuvant chemotherapy followed by complete surgical resection.\textsuperscript{23} When counseling patients about their options, it is important to balance the morbidity that is often inherent in complete surgical resection and organ preservation that is potentially afforded by early use of chemotherapy.

Those with high risk of recurrence—as defined by large tumor size, positive margins, and tumor capsule rupture—are candidates for adjuvant chemotherapy and radiation. Postoperative follow-up includes regular imaging and biomarker analysis.

There have been multiple studies aimed at characterization of ACC tumor biology in hopes of defining molecular targets for therapy, disease prediction, and prognostication. Techniques such as next-generation sequencing and RNA interference are changing how we look at tumor biology and the information we can provide our patients. For example, while not yet clinically used, tumor microRNA analysis appears to provide important prognostic and diagnostic value in terms of disease progression, recurrence,
and survival. As we become more sophisticated in our characterization, we stand to improve our clinical fidelity and decision making.

**Miscellaneous.** Simple cystic lesions are usually incidental, and surgery is not indicated unless there is a solid component to the cyst wall. Complex cysts with evidence of local invasion should undergo open resection. Large cysts that cause symptoms or that carry a high risk of spontaneous rupture can be excised by laparoscopic nodulectomy or subjected to fenestration of the cyst wall into the peritoneal cavity.

Myelolipomas are also typically discovered in an incidental manner. Their appearance can cause confusion with liposarcoma, a situation easily resolved with needle biopsy showing typical bone marrow elements. Patients with these benign adrenal lesions are often referred to surgery because of compressive symptoms.

**Diseases of the Medulla**

**PHEOCHROMOCYTOMA**

*Pheochromocytomas* are rare neuroendocrine tumors that are derived from chromaffin cells and usually arise from the adrenal medulla. Although most pheochromocytomas are sporadic and unilateral, genetic syndromes such as multiple endocrine neoplasia 2a/2b and von Hippel–Lindau increase the risk of bilateral disease. They can produce catecholamines such as epinephrine, norepinephrine, and dopamine that can cause the classic clinical symptomatology of this disease: episodic headaches, palpitations, and diaphoresis. Rarely, pheochromocytomas are nonfunctional.

The Endocrine Society recently published practice guidelines for the evaluation and management of pheochromocytoma/paraganglioma. The biochemical diagnosis can be made with either fractionated urine catecholamines (24-hour collection) or serum metanephrines (*Table 78-2*). Due to the high level of false positive results, plasma metanephrine testing should be completed in patients with a high pretest probability. Furthermore, at least a fourfold elevation of these biochemical tests should be expected from symptomatic pheochromocytoma. Surgeons should be aware that many medications could influence these biochemical tests, which include, but are not limited to, acetaminophen, β-blockers, vasodilators, α-
blockers, stimulants, antipsychotics, antidepressants, and calcium channel blockers. Equivocal results should prompt repeat testing after holding these medications. Marginal elevations in biochemical tests are unlikely to be driven by pheochromocytoma. Clinical context is important for diagnosis, since pheochromocytoma can be excluded with confidence when testing results are normal in a hypertensive and symptomatic patient. Equivocal results should prompt repeat testing after holding these medications. Marginal elevations in biochemical tests are unlikely to be driven by pheochromocytoma. Clinical context is important for diagnosis, since pheochromocytoma can be excluded with confidence when testing results are normal in a hypertensive and symptomatic patient.25 Borderline serum metanephrine elevations less than fourfold warrant repeat testing after 30 minutes of supine rest.

CT imaging is similar to that for ACC—tumors tend to be large, heterogeneous, solitary, hypervascular, and greater than 10 Hounsfield units.4 Pheochromocytomas typically have a characteristic intensity on T2-weighted MRI. This is an ideal imaging modality for patients with surgical clips that cause artifacts on CT, in patients with an allergy to iodinated contrast agents, and in patients who cannot receive ionizing radiation. Metaiodobenzylguanidine (MIBG) enables scintigraphic functional imaging of the whole body, which is useful when familial, extradrenal, or metastatic disease is suspected. Rarely, MIBG can be useful in the final diagnosis of equivocal cases. MIBG scanning is not as sensitive as FDG-PET CT for finding extraadrenal tumors and metastatic disease. In patients with metastatic pheochromocytoma, I123-MIBG scanning can also be useful to determine whether future high-dose I131-MIBG can be a treatment option.28

Preoperative preparation with α-blockade (eg, phenoxybenzamine, doxazosin) and salt loading should be undertaken. Ideally, this can be done in the outpatient setting. The α-blocker is titrated up to the maximal tolerated dose, which is typically limited by orthostatic hypotension. Salt loading, either by ingestion of salty foods or by saline infusion, can help to reduce orthostasis and enable higher doses of α-blocker. In addition, β-blockade can be added to the regimen if the patient has persistent tachyarrhythmias. Although the optimal preparation time before pheochromocytoma resection is controversial, we generally α-block and salt-load patients for 1 to 2 weeks before elective adrenalectomy and operate only after orthostatic hypotension is achieved.

Delicate tissue handling and avoidance of tumor compression should be emphasized to minimize catecholamine release. Because tumor manipulation and adrenal vein clipping can result in significant hemodynamic changes, coordination and communication between the adrenal surgeon and anesthesiologist are critical to the success of this operation. It has been
generally proposed that in the resection of pheochromocytomas ligation of the adrenal vein should precede the rest of the dissection to limit hemodynamic instability. However, delayed ligation of the vein has been shown to result in a similar rate of intraoperative hypertension and concentration of plasma catecholamines when compared with early ligation.\textsuperscript{29,30} Further, some authors caution that adrenal vein ligation increases intratumor venous pressure, which can increase bleeding.\textsuperscript{29} In our practice we have found that grasping the tumor side of the divided adrenal vein to be quite helpful. Regardless of the decision on timing of ligation, communication between the surgical and anesthesia teams is imperative because hypotension often accompanies vein ligation.

**Paraganglioma**

Paragangliomas are neuroendocrine tumors histologically similar to pheochromocytomas but that occur in extra-adrenal sites throughout the pelvis, abdomen, chest, neck, and head. Most of these tumors are sporadic, although some are associated with hereditary paraganglioma syndromes. They typically present as a painless mass or with the symptomatology of a pheochromocytoma resulting from catecholamine production. There are several case reports of successful laparoscopic resection of these tumors, but the decision to pursue laparoscopy again is determined by location and size of the paraganglioma.\textsuperscript{31–33}

**Peripheral Nerve Sheath tumors**

Schwannomas are rare and benign lesions that originate from the Schwann cells of peripheral nerve sheaths. They are occasionally encountered in the periadrenal or perirenal area and can mimic ACC or renal cell carcinoma in both preoperative imaging and in presentation due to compression of nearby structures.\textsuperscript{34–39} Retroperitoneal schwannomas represent roughly 0.3% to 3% of all schwannomas and 4% of all retroperitoneal tumors.\textsuperscript{37,39,40}

While many schwannomas are diagnosed only after resection in patients experiencing compressive symptoms or for concern of other primary malignancy, there are characteristic findings that may allow preoperative diagnosis. They tend to be well-circumscribed, do not invade surrounding
structures, they have central cystic degeneration with peripheral enhancement, are isointense on T1- and T2-weighted MRI, and are hyperintense compared to skeletal muscle. Core needle biopsy can reliably establish the diagnosis. On gross examination, they tend to be firm, fibrous, and white. They should be resected if they cause compressive symptoms. A small number of these tumors undergo malignant transformation and thus all preoperatively diagnosed schwannomas should have close surveillance.40

Metastasis

Resection of adrenal metastases is controversial, and the role for surgical treatment is changing now that safe minimally invasive resection can be achieved with minimal morbidity. Although no prospective trials have proven that adrenal metastasectomy improves survival, many groups have reported safe laparoscopic resection of various secondary tumors, such as lung, renal cell, colorectal, gastric, ovarian, breast, and melanoma primaries.41−45 Generally speaking, patient selection for metastasectomy should favor the following: (1) oligometastases, (2) metachronous lesions, (3) tumor response to systemic chemotherapy, and (4) good patient performance status.

CHOOSING THE OPTIMAL PROCEDURE

Laparoscopic versus Open Adrenalectomy

Since the first laparoscopic adrenalectomy in 1992,46 multiple case series have compared endoscopic to open surgery. Most analyses show that laparoscopic adrenalectomy is associated with decreased length of hospital stay, decreased postoperative pain, and overall decreased morbidity.47−52 In analyzing 669 adrenalectomies (358 laparoscopic and 311 open), Lee et al. showed that open surgery was associated with longer operative time (3.9 vs. 2.9 hours), higher transfusion rate, more reoperations (4.8 vs. 1.4%), longer length of stay (9.4 vs. 4.1 days), and higher 30-day morbidity rate (17 vs. 3.6%) even after adjusting for cofounding factors.53 Thus, for the treatment of small, benign disease, or functional tumors, laparoscopy is the method of choice. Many groups have reported that tumors greater than approximately 10
to 12 cm should be resected with open surgery.47,54–56

A randomized controlled trial of laparoscopic versus open adrenalectomy for pheochromocytoma found no significant differences in hemodynamic instability between the two groups, but operative time and blood loss were favored in the laparoscopic group.51 Thus, endoscopic adrenalectomy is the favored procedure when there is no evidence of malignant disease.56 However, conversion to an open procedure should be considered whenever there is difficulty achieving gross tumor clearance or capsular disruption seems imminent during endoscopic dissection.

An early observational study by Gonzalez et al. aimed at identifying the efficacy of laparoscopic surgery for the management of ACC showed that in laparoscopy the peritoneal recurrence was 83% (n = 6) compared to 8% (n = 133) in open transabdominal adrenalectomy. All tumors in this study were less than or equal to 8 cm and nonadherent to adjacent structures. Of note, all the laparoscopic procedures were performed at a separate institution prior to referral to the index center.22 As a result of this study, open surgery became the standard when ACC is strongly considered (transverse diameter >4-6 cm and heterogeneity).22,57 Recently, this paradigm has been challenged—especially at high-volume centers—with the success laparoscopic resection of malignant adrenal disease.18,58,59 Donatini et al. showed that there was a decrease in postoperative morbidity but no difference in overall survival in patients who underwent laparoscopic section for stage I or II ACC with tumor size less than 10 cm as compared to open adrenalectomy.60

At our institution, we do not attempt minimally invasive adrenalectomy when local invasion is determined on preoperative imaging. Intraoperative difficulty with establishing tissue planes between the adrenal gland and neighboring structures, due to tumor extension, portends malignancy and should prompt immediate conversion to open adrenalectomy.

In contrast to patients who require attempted curative resection of primary ACC, it is reasonable to consider endoscopic palliative adrenalectomy of primary tumors and metastases. Strong et al. report equivalence between laparoscopy and open surgery in terms of local recurrence, disease-free interval, and overall survival.61 Furthermore, there is a role for palliative laparoscopic resection for patients with symptomatic secondary tumors. Attempts at laparoscopic metastasectomy should be avoided in any patient with radiographic evidence of local invasion, as complete resection without
capsular disruption is unlikely.

**Retroperitoneoscopic**

The posterior retroperitoneoscopic (RP) approach has quickly gained traction as an alternative, minimally invasive method to adrenal surgery that offers a more direct route to the retroperitoneal glands. This approach is usually performed in nonobese patients who have smaller lesions. Further, it is favored for bilateral lesions, as repositioning is not necessary. The posterior approach is particularly useful for patients with adrenal disease who have undergone prior abdominal surgery, since these patients might have dense adhesions that make an intra-abdominal exposure formidable.

A few anthropometric parameters have been correlated with successful RP surgery: (1) less than 5 cm distance from Gerota’s fascia to the skin, (2) the 12th rib at or rostral to the renal hilum. Further, many surgeons will not perform RP surgery in obese patients given the difficulty with positioning and ventilation. However, this has been recently challenged. Epelboym and colleagues showed a decreased length of stay in patients with BMI >30 who were offered a posterior laparoscopic as compared to a transperitoneal approach.

Walz et al. retrospectively analyzed 560 consecutive RP adrenalectomies performed from 1994 to 2006 for tumors ranging from 0.5 to 10 cm. They showed that this approach was safe (1.3% major complication, 14.4% minor complication, and 0% mortality rate) when performed by an experienced surgeon. Furthermore, when compared with transperitoneal laparoscopic adrenalectomy, the RP approach has been shown to take less time, result in less—albeit not likely clinically significant—blood loss, and is associated with fewer conversions to an open procedure.

**Partial Adrenalectomy**

Partial adrenal resection has the perceived benefit is sparing of the necessity of steroid replacement. Multiple small studies have found this approach a reasonable alternative procedure for benign, well circumscribed, and peripherally located tumors. In a small, randomized clinical trial of RP total versus partial adrenalectomy for aldosterone-secreting adenomas, Fu et
al. showed essentially noninferiority of partial adrenalectomy in terms of postop complications and functional outcome. There was a statistically significant but clinically irrelevant increase in operative blood loss in the partial adrenalectomy group.\textsuperscript{68}

While some studies have shown benefit, Quillo et al. showed that in nearly 21\% of patients undergoing total unilateral adrenalectomy for hyperaldosteronism, there was additional hyperfunctional tissue. Further, they were unable to identify any preoperative predictors of having non-solitary versus solitary adenomas.\textsuperscript{69} Thus, given the significant risk of missing an additional functional adenoma during partial adrenalectomy, most surgeons opt for a total adrenalectomy.

From a technical perspective, partial adrenalectomy is carried out in a similar way to total adrenalectomy as far as positioning and steps of dissection. While in general, preservation of the adrenal vein is recommended, division has been shown not to be detrimental to the function of the gland.\textsuperscript{47}

**EXPOSURES AND OPERATIVE TECHNIQUE**

**General Considerations**

First, any bleeding substantially impairs visualization. Dissection should be gentle and every act of tissue division accompanied by a hemostatic maneuver. Second, obscuring blood is difficult to evacuate, and thus it tends to accumulate and obscure the bed of dissection. Third, removal of blood by suction tends to collapse the operative field and lead to tedious adjustment of retraction. For these reasons, we recommend small neurosurgical patties or rolled Kitner sponges to remove blood and to control minor bleeding. The use of instruments with hemostatic capability, such as ultrasonic shears or bipolar vessel sealing devices, can shorten operative times and make the use of clips or ligatures unnecessary. Fourth, patients with wide hips impair manipulation of instruments through the most lateral port. Port sites should be placed at least 7 cm apart to avoid limitations from instrument crowding. Finally, retraction of the adrenal can cause rupture and bleeding. When possible, retract the gland by touching the periadrenal fat rather than applying force to the capsule of the gland. The specimen side of the adrenal vein after ligation
can also be used as a handle for retraction. Otherwise, a rolled Kitner sponge held with a grasper can provide gentle and effective traction.

For retraction we recommend using a fan retractor. This is an adjustable broad-based, atraumatic instrument that provides excellent retraction on larger organs like the liver and smaller areas like the peridrenal fat. When combined with hook cautery or LigaSure™, the surgeon has the ability to be expedient around the lateral liver edge and precise around the IVC.

**Positioning**

As in all operations, patient positioning and exposure are critical to the success of adrenalectomy. The details of the positioning depend upon the approach selected.

Figure 78-1 depicts the positioning for the laparoscopic transperitoneal approach. Patients are placed in the lateral decubitus position, which favors retraction of the abdominal viscera by gravity and facilitates exposure of the adrenal gland. We use a pneumatic beanbag to help secure patients in the proper position. In obese patients, it may be useful to position the anterior border of the patient’s body near the edge of the bed and allow the abdominal pannus to hang over the edge. Of note, the hips should be relatively open as compared to the shoulders.
FIGURE 78-1 Optimal positioning of patient for a left laparoscopic adrenalectomy in the lateral decubitus position. The midabdomen is placed over the break in the table to optimize trunk extension and reduce interference with instrument movement by the iliac crest. The anterior abdominal wall should not be compressed.

To facilitate exposure, the surgical table should be flexed and a kidney bar elevated with the apex located slightly higher than the midpoint between the costal margin and the iliac crest. Care should be taken during flexion in the elderly and in patients with spine disease. The patient should be secured to the table with wide tape, an axillary roll placed, and all pressure points should
be adequately protected, including the peroneal nerves.

When preparing for RP adrenalectomy, the endotracheal tube and intravenous, arterial, and Foley catheters are placed with the patient in the supine position. The patient is then flipped into the prone position, with the hips and knees flexed. This positioning requires the use of bolsters across the chest and hips, as well as sufficient padding for the face, arms, and knees. The abdomen should hang down between the two transversely positioned bolsters.

**Laparoscopic Adrenalectomy**

**RIGHT LAPAROSCOPIC ADRENALECTOMY**

**Step 1: Port Positioning.** The patient is placed in the left lateral decubitus position, and the surgeon marks four port sites along the right costal margin from the xiphoid to the midaxillary line. Either a Veress needle entry or a muscle-splitting open entry can be used to gain access to the peritoneal cavity. After insufflation of the peritoneal cavity and placement of additional ports under direct vision, the fan retractor is placed in the most medial port and the camera is placed in the second most medial port (Fig. 78-2).
FIGURE 78-2 Port placement for a right laparoscopic adrenalectomy. In this example, abdominal entry is gained under direct visualization through the most medial site.

**Step 2: Expose the Retroperitoneum.** The hepatic flexure of the colon is
freed from its attachments and allowed to retract inferomedially by gravity (Fig. 78-3). The fan retractor initially retracts the right lobe of the liver in the medial direction, and the right triangular ligament is taken down with a hook electrocautery (Fig. 78-4). This mobilization enables superior and anterior retraction of the right lobe of the liver, which uncovers the retroperitoneum near the adrenal gland (Fig. 78-5). In most cases, the kidney, periadrenal fat, and IVC are visible after this maneuver (Fig. 78-6).

**FIGURE 78-3** Initial view of right upper quadrant in a right laparoscopic adrenalectomy. The *arrow* indicates the direction of liver retraction from the epigastric port.
FIGURE 78-4  View during right laparoscopic adrenalectomy with the liver retracted from the epigastric port. Some attachments of the right lobe of the liver to the diaphragm have been divided. The dotted line indicates the line of further peritoneal incision to mobilize the right lobe of the liver from the diaphragm.
FIGURE 78-5  View during right laparoscopic adrenalectomy after initial dissection to mobilize the right adrenal. The dotted line shows the peritoneal incision under the retracted liver that exposes the adrenal.
FIGURE 78-6 Dissection to expose the adrenal gland during right laparoscopic adrenalectomy.

**Step 3: Approach the Adrenal Gland.** We begin the dissection in the superolateral border of the periadrenal fat with a hook electrocautery. This exposes the diaphragm posteriorly, and the dissection is carried out in the medial direction along the superior border of the periadrenal fat. A few small arteries are typically located in this area, which can be controlled with electrocautery or a hemostatic device. Careful dissection with blunt graspers should be used while approaching the IVC, near the superomedial border of the periadrenal fat.

**Step 4: Divide the Adrenal Vein.** After establishing the superomedial corner of the periadrenal fat, the dissection is carried down in the caudal direction between the IVC and periadrenal fat. The tissue plane between the IVC and the adrenal vein is extremely thin, and thus blind use of hook cautery should be avoided. We prefer to use a combination of gentle, blunt dissection and the LigaSure device. The adrenal vein typically resides near the top third of this medial border and approaches the IVC at approximately a right angle. After
clip or stapler ligation of the adrenal vein, this medial plane of dissection opens significantly (Fig. 78-7). Notably, some surgeons routinely divide the adrenal vein with the LigaSure device without the use of a clips or staples.

**FIGURE 78-7** Dissection to expose the adrenal vein during right laparoscopic adrenalectomy. The length of the right adrenal vein is exaggerated in this schematic.

**Step 5: Dissect the Adrenal Gland from the Retroperitoneum.** At this point, the specimen side of the adrenal vein can be grasped for retraction. The inferomedial border of the dissection also requires careful blunt dissection, with special attention to avoid injuring the renal hilar vessels. The dissection is then carried laterally along the superior surface of the kidney. Special care must be taken to avoid accidental ligation of any arterial branches to the superior pole of the kidney. Once the plane of dissection is established between the inferior border of the periadrenal fat and the kidney, the only remaining attachments are posterior and lateral to the adrenal gland. A blunt grasper can be used to elevate the adrenal gland in the anterior direction, with special care taken to avoid disruption of the adrenal capsule. The remaining
posterior and lateral attachments can be divided with a LigaSure or Harmonic scalpel device. The dissection should clear all fibro-fatty and lymphatic tissue from the diaphragmatic surface.

**Step 6: Removal of the Adrenal Gland.** Once all attachments are divided, the gland is placed into an endoscopic bag for removal. If appropriate, the mouth of the bag can be exteriorized and the specimen can be morcellated and removed through a port incision. This maneuver should always be performed under laparoscopic vision, as opposed to blind morcellation. Alternatively, the specimen can be removed intact and en bloc, which typically requires dilation of the fascia and skin.

**LEFT LAPAROSCOPIC ADRENALECTOMY**

**Step 1: Port Placement.** The patient is placed in the right lateral decubitus position and the surgeon marks three or four port sites along the costal margin from the xiphoid to the posterior axillary line. Sometimes the fourth port is not needed, as the spleen retracts medially with gravity (Fig. 78-8).
Step 2: Expose the Retroperitoneum. The splenic flexure of the colon is taken down (Fig. 78-9). The left liver and spleen are mobilized from the diaphragm using hook electrocautery. With medial mobilization of the spleen, the retroperitoneum is exposed. The left kidney, periadrenal fat, and tail of the pancreas are often visualized at this point.
FIGURE 78-9  View during left laparoscopic adrenalectomy, showing division of the peritoneum over the kidney and progressive detachment of the spleen from the left diaphragm.

Step 3: Approach the Adrenal Gland. The dissection begins in the superolateral corner and proceeds in the medial direction between the spleen and the superior border of the adrenal gland. The splenic vessels are often in close proximity to this plane of dissection. Once the superomedial corner is reached, the tail of the pancreas and the inferior phrenic vein can often be seen. Note that the pancreas tail can appear similar to the adrenal gland (Fig.
FIGURE 78-10 View during left laparoscopic adrenalectomy. The spleen had been partially mobilized and is retracting to the right by gravity. The separation between the posterior pancreas and the anterior surface of the left adrenal had been developed. The left renal vein is exposed, as well as the takeoff of the left adrenal vein.

**Step 4: Divide the Adrenal Vein.** The dissection continues in the inferior direction along the medial border. The inferior phrenic vein can be used as an anatomic landmark and can be divided if necessary. The left adrenal vein is often located in the inferomedial portion of the dissection and often joins the inferior phrenic vein prior to joining with the renal vein (Fig. 78-11).
FIGURE 78-11 View during left laparoscopic adrenalectomy. The spleen is fully mobilized. The adrenal vein has been divided between endoclips. The dotted line indicates the line of resection.

Step 5: Dissect the Adrenal Gland from the Retroperitoneum. After adrenal vein ligation, the dissection continues along the inferior border between the adrenal gland and the kidney. In a similar fashion to the right adrenalectomy, the remaining posterior and lateral attachments are divided flush to the surface of the kidney and diaphragm, and the adrenal tumor is removed in bloc with the surrounding periadrenal fat. Again, the specimen side of the divided adrenal vein can be grasped as a handle for retraction.

RETROPERITONEOSCOPIC
Step 1: Port Placement. A small transverse incision is made just caudal to the tip of the 12th rib, and sharp dissection is used to dissect through the subcutaneous tissues and deep fascia. The length of this incision should be around 1.5 cm, which should be enough to accommodate the surgeon’s index finger. Digital examination with the index finger can be used to confirm that the dissection is through the deep fascia, and it allows palpation of the smooth underside of the ribs. Some authors recommend placement of the trocars 1 to 2 cm caudal to the 12th rib to prevent neuralgia. A second lateral 5-mm port is placed at near the midaxillary line at the same craniocaudal level under direct palpation, using the index finger as a guide through the first incision. Then a third 5-mm port is placed similarly under digital palpation, just lateral to the paraspinous muscles at the same craniocaudal level. This medial port should be approximately 3 or 4 cm caudal to the lowest rib. Then a 12-mm balloon port is placed in the middle incision to ensure an airtight seal. The space is insufflated to a pressure of 20 to 30 mm Hg. A 30-degree 10-mm scope is placed in the middle trocar with the angled view facing the ceiling.

Step 2: Expose the Peritoneal Lining. A blunt grasper is used though the lateral port to dissect through the Gerota fascia. Using blunt dissection, the tissues around the medial and lateral ports are cleared and space is created posterior to the kidney and adrenal gland. Usually, the paraspinous muscles can be seen medially. With some blunt dissection, the peritoneal lining can be visualized laterally. Inferiorly, at the floor of the dissection (anterior), careful blunt dissection can be used to visualize the kidney.

Step 3: Approach the Adrenal Gland. Dissection is carried along the superior border of the kidney from lateral to medial to separate the top of the kidney from periadrenal fat and to mobilize the kidney off the peritoneum such that it autoretracts inferiorly, which is necessary to expose the inferomedial portion of the adrenal gland. Usually during this portion of the dissection, the adrenal gland itself becomes evident through the periaireadrenal fat. On the right side, the IVC is found anterior and medial to the inferomedial border of the periaireadrenal fat.

Step 4: Divide the Adrenal Vein. The adrenal vein is usually anterior and thus can be difficult to visualize. In contrast to the laparoscopic approach, the
adrenal vein is seen relatively late in the dissection when performing an RP adrenalectomy. Division of the adrenal vein can be done with a LigaSure device with or without clips. The specimen side of the adrenal vein can be used to retract the adrenal gland in the cephalad and posterior directions.

**Step 5: Dissect the Adrenal Gland from the Retroperitoneum.** The remaining attachments between the periadrenal fat anteriorly and superiorly can be divided with a LigaSure device or electrocautery.

**Step 6: Removal of the Adrenal Gland.** Removal of the specimen can usually be achieved without morcellation or extension of the incision. Closure of the deep fascia in the middle incision usually requires only a single simple nonabsorbable suture. Hernia through these posterior incisions is uncommon.

As with laparoscopic adrenalectomy, the small adrenal arteries can be controlled with either hook electrocautery or a hemostatic device; clips are usually not required. Small holes in the peritoneum are of no significant consequence and do not require repair.

**Open Adrenalectomy**

**ANTERIOR**

The anterior approach allows access to both adrenal glands as well as extra-adrenal foci as in the case of pheochromocytoma. The patient is placed in the supine position on the operating table, and either a midline laparotomy or bilateral subcostal incision can be used. We find that the subcostal incision is adequate but the exposure is not as open as in the thoracoabdominal approach (below).

For right-side access, the hepatic flexure of the colon is taken down inferiorly, the liver is retracted superiorly, and a Kocher maneuver is performed to expose the retroperitoneal space. The Gerota fascia is identified and incised. Once the adrenal gland is exposed, the lateral and superior aspects of the gland are mobilized and the adrenal vein is ligated and divided. Given the proximity of the right adrenal gland to the IVC, the surgeon must use care when dissecting and ligating the right adrenal vein.

The left adrenal gland can be exposed from an anterior approach by a
medial visceral rotation of the stomach, spleen, splenic flexure of the colon, and pancreas toward the midline. The left adrenal vein can drain either into the left renal vein or the left inferior phrenic vein. The remainder of the dissection is similar to the right side.

**Thoracoabdominal Approach**

For open adrenalectomy, we prefer the thoracoabdominal approach due to the superior exposure that it allows, the close proximity of the incision to the lesion, and the improved ability to remove large tumors. Much like in the laparoscopic approach, the patient is placed in the lateral decubitus position with the hips open and the shoulders closed. The shoulders should be roughly 90 degrees to the table.

The dissection is carried down between the eighth and ninth ribs, allowing the full exposure of the adrenal gland, renal fossa, and surrounding tissues. A vascular load GIA stapler is used to divide the diaphragm close to the lateral attachments, which facilitates closure at the end of the case. The remainder of the dissection is carried out as mentioned previously. A tube thoracostomy should be placed or the pneumothorax can be evacuated during closure.

**RETROPERITONEAL**

In this operation, the patient is placed in the prone position on the operating table, and a curvilinear incision is made starting in the paramedian line and extending laterally. After the skin and subcutaneous tissues are incised, the latissimus dorsi muscle is divided with electrocautery near its origin and the serratus posterior is divided in a similar way. The 12th rib is removed to facilitate the exposure, and the 11th rib and the pleura are retracted superiorly, which exposes the underlying the Gerota fascia. The fascia is incised, and the adrenal gland and the kidney are exposed. The superior vessels are ligated and divided, and the superior aspect of the gland is dissected free. After the gland is mobilized, the adrenal vein is isolated, ligated, and divided. When the gland has been removed, closure is performed in layers.

**COMPLICATIONS**
The intraoperative risks of adrenal surgery are due largely to the close proximity to large vascular structures and other retroperitoneal organs. Consequently, minimally invasive adrenalectomy poses the same anatomic risks as open adrenalectomy: major vascular injury (IVC, splenic vessels, renal vessels) and injury to the spleen, liver, and colon. Although rare, transection of the porta hepatis, hepatic artery, ureter, and renal artery has been reported.\(^7\)

Pneumoperitoneum poses several risks for this operation aside from traumatic injury relating to port placement. The dissection of the adrenal gland is in close proximity to the posterior aspect of the diaphragm, making ipsilateral pneumothorax a potential complication necessitating a tube thoracostomy in some. Further, pneumoperitoneum can impair venous return, which can be particularly dangerous in the setting of catecholamine surges during resection of pheochromocytoma. This risk can be minimized with pre- and intraoperative hydration. The spleen and liver are also at risk for injury during laparoscopic adrenalectomy; these organs can sustain trocar injuries, capsular tears from grasping or retraction, or vascular injury.

The most life-threatening complication of adrenalectomy is a vascular injury. On the right, the renal vein can have an oblique course and course through the inferior portion of the dissection, causing confusion with the adrenal vein. The right adrenal vein is often well visualized with laparoscopic technique but is also of variable location in a superior-inferior plane and anterior-posterior plane. A vein with a diameter significantly smaller than the length of a standard endoscopic clip should be viewed with skepticism if thought to be the adrenal vein. A vein with a diameter significantly larger than an endoclip or that does not clearly connect to the variegated dark yellow adrenal gland is a suspect for the renal vein and should not be divided without certain identification. On the left, there can be a segmental upper pole renal artery that lies just deep to the lower portion of the adrenal. The adrenal arteries are all quite narrow and can be ligated with the electrocautery or vessel-sealing device without the use of clips. Regarding RP adrenalectomy, higher insufflation pressures are tolerated well with less hemodynamic compromise, in comparison to the laparoscopic technique. Releasing insufflation and hyperventilating the patient can relieve intraoperative hypercarbia. Subcutaneous emphysema and subcostal nerve dysfunction can be observed after RP adrenalectomy, and both are transient in nature.

Hypoglycemia is a well-recognized complication in adrenalectomies performed for pheochromocytoma. In our experience, roughly 4% of patients...
develop blood glucose levels less than 50 mg/dL, thought to be due to rebound hyperinsulinemia. This most often occurs in the first 24 hours and is associated with higher 24-hour urinary metanephrine levels, longer operative times, and larger neoplasms.\(^7\)

In an effort to identify correctable causes of post-adrenalectomy complications, Hauch et al. performed a cross-sectional analysis of 7829 adrenalectomies included in the Nationwide Inpatient Sample from 2003 to 2009. They found that surgeons performing less than five adrenalectomies per year were more likely to have pulmonary, cardiovascular, bleeding, and technical complications than their counterparts performing greater than five adrenalectomies per year. Similarly, there were more complications seen in bilateral operations and those for malignancy.\(^7\)

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